

Subtotal Parathyroidectomy as an Adequate Treatment for Primary Hyperparathyroidism in Multiple Endocrine Neoplasia Type 1

Johnathan G. H. Hubbard, MD, FRCS; Frederic Sebag, MD; Sylvie Maweja, MD; Jean-Francois Henry, MD

Hypothesis: The most appropriate surgical approach for hyperparathyroidism (HPT) in multiple endocrine neoplasia type 1 remains controversial. It has been advocated that reoperations for recurrent disease are easier to perform after total parathyroidectomy (TP) with autotransplantation than after subtotal parathyroidectomy (SP). In view of our large experience in patients with secondary HPT for whom TP with autotransplantation did not simplify reoperations, SP remains our preferred treatment for patients with HPT and multiple endocrine neoplasia type 1.

Design: Retrospective cohort study.

Setting: Tertiary referral medical center.

Patients: A total of 29 consecutive patients (22 women, 7 men; mean age, 42.2 years) with multiple endocrine neoplasia type 1 who underwent definitive cervical exploration for HPT.

Main Outcome Measures: Temporary and permanent hypocalcemia, pattern of parathyroid disease, and sites and timing of recurrent HPT. Definitive primary surgery included SP in 21 patients, TP with autotransplantation in 4 patients, and less-than-subtotal parathyroidectomy in 4 selected patients.

Results: The mean follow-up was 88.5 months (range, 8-285 months). Four patients died during follow-up; 2 of these deaths were related to multiple endocrine neoplasia. No patients had persistent HPT. Temporary hypocalcemia occurred in 12 SP cases (57%), 4 TP with autotransplantation cases (100%), and 0 less-than-subtotal parathyroidectomy cases. Permanent hypocalcemia requiring long-term treatment occurred in 2 SP cases (10%), 1 TP with autotransplantation case (25%), and 0 less-than-subtotal parathyroidectomy cases. Four patients developed recurrent disease, including 1 with SP, 2 with TP with autotransplantation, and 1 with less-than-subtotal parathyroidectomy at 57 months, 197 and 180 months, and 164 months, respectively, representing 14% of all of the patients and 43% of patients with more than 10 years of follow-up.

Conclusions: Recurrent HPT occurs many years after definitive primary surgery (median, 14.3 years). Surgical treatment should therefore aim to minimize the risk of permanent hypocalcemia and facilitate future surgery. When correctly performed, SP fulfills these objectives.

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HYPERPARATHYROIDISM (HPT) is the most common, and frequently the first, manifestation of the autosomal dominant inherited multiple endocrine neoplasia type 1 (MEN 1) syndrome, which frequently also involves tumors of the pituitary and pancreas. In MEN 1, HPT generally appears at a younger age than in sporadic HPT, and the underlying pathological abnormalities and natural courses differ.

Germline mutations in the tumor suppressor gene *MEN1* are responsible for MEN 1. Expression of the *MEN1* gene is most marked in actively proliferating cells and is found in both endocrine and non-endocrine tissue. *MEN1* encodes for the 610-amino acid protein menin, which has a wide range of interactions that are under investigation.¹

In MEN 1, HPT typically results in hyperplasia of multiple parathyroid glands. Recently, the possibility of sequential adenoma formation following double hits of the *MEN1* gene² has also been suggested. The heterogeneity of parathyroid gland size in MEN 1 is well recognized,^{3,4} and supernumerary glands are common (20%-30%).⁵⁻⁷ These patients are thus at risk of inadequate initial surgery, especially if MEN 1 is not suspected before or at the time of the surgical procedure, and are at increased risk of recurrent HPT owing to the long-term evolution of residual parathyroid tissue.

There has been controversy as to the most appropriate surgical approach for HPT in MEN 1. Surgical approaches have tried to minimize the risks and need for reoperative surgery as well as the long-term risks of hypocalcemia in younger pa-

Author Affiliations:

Department of Endocrine Surgery, University Hospital La Timone, Marseille, France. Dr Hubbard is now with the Department of General and Endocrine Surgery, St Thomas' Hospital, London, England, and Dr Maweja is now with the Department of General and Endocrine Surgery, Centre Hospitalier Universitaire Sart Tilman, Liege, Belgium.

Table 1. Features of Multiple Endocrine Neoplasia Type 1

| Patient | Surgical Procedure (Year) | Biopsied Glands, No. (Pathological Glands, No./Type) | Family History of MEN 1 | Other Features | Deceased |
|---------|-------------------------------------|--|-------------------------|----------------------------------|----------|
| 1 | SP (1974) | 3 (2/H) | No | Pituitary | Yes |
| 2 | TP with autotransplantation (1985) | 4 (4/H) | No | Pituitary and pancreas | Yes |
| 3 | LSP (1979) | 3 (1/A) | No | Pancreas | No |
| 4 | TP with autotransplantation (1985) | 4 (4/H) | No | Pituitary, pancreas, and adrenal | No |
| 5 | TP with autotransplantation (1985) | 4 (4/H) | Yes | Pancreas | No |
| 6 | TP with autotransplantation (1985)* | 2 (2/H)† | No | Pancreas | No |
| 7 | SP (1987) | 4 (1/H, 1/A) | No | Pituitary and pancreas | Yes |
| 8 | SP (1989) | 4 (4/H) | No | Pituitary | No |
| 9 | LSP (1988) | 3 (1/A) | No | Pituitary | No |
| 10 | SP (1993) | 4 (2/H) | Yes | Pituitary | No |
| 11 | SP (1994) | 4 (4/H) | Yes | NA | Yes |
| 12 | LSP (1995) | 2 (2/H) | No | Pituitary | No |
| 13 | SP (1991) | 4 (4/H) | Yes | Pituitary | No |
| 14 | SP (1995) | 4 (4/H) | Yes | Pituitary | No |
| 15 | SP (1996)* | 2 (2/H)† | Yes‡ | Pancreas | No |
| 16 | SP (1996) | 3 (1/H, 1/A) | Yes | NA | No |
| 17 | SP (1997) | 4 (4/H) | Yes | Pituitary, pancreas, and adrenal | No |
| 18 | SP (1997) | 4 (4/H) | Yes‡ | Pancreas | No |
| 19 | SP (1999) | 4 (4/H) | No | Pituitary and pancreas | No |
| 20 | SP (1999) | 4 (2/H) | No | Pituitary | No |
| 21 | LSP (1999)§ | 2 (NA) | Yes | Pancreas and adrenal | No |
| 22 | SP (1999) | 4 (4/H) | No | Pituitary | No |
| 23 | SP (2000) | 4 (4/H) | Yes | Pancreas | No |
| 24 | SP (2000) | 4 (3/H) | Yes | NA | No |
| 25 | SP (2001) | 4 (2/H) | No | Pituitary | No |
| 26 | SP (2001) | 5 (4/H) | Yes | NA | No |
| 27 | SP (2001) | 4 (4/H) | No | Pituitary | No |
| 28 | SP (2002) | 3 (2/H) | No | Pituitary | No |
| 29 | SP (2002) | 3 (2/H) | Yes‡ | NA | No |

Abbreviations: A, adenoma; H, hyperplasia; LSP, less-than-subtotal parathyroidectomy; MEN 1, multiple endocrine neoplasia type 1; NA, not applicable; SP, subtotal parathyroidectomy; TP, total parathyroidectomy.

*Definitive procedure following first procedure (excision of 2 glands) elsewhere.

†Two glands were previously excised.

‡Confirmed *MEN1* mutation.

§Patient underwent LSP elsewhere.

tients. Surgical options include total parathyroidectomy (TP) with autotransplantation of tissue to the arm to avoid reoperative neck surgery, subtotal parathyroidectomy (SP), and lesser forms of parathyroid excision.

Investigations such as the Casanova test⁸ have been devised to distinguish between graft and neck recurrence following TP with autotransplantation. However, our experience with TP with autotransplantation in patients with secondary HPT⁹ has suggested that determining the site of recurrence and the treatment of recurrent disease in transplanted tissue is not always straightforward. Therefore, SP as defined in this article remains our preferred method of treating MEN 1–related HPT. In this article, we review our experience of treating HPT in this group of patients.

METHODS

Between November 1974 and April 2002, 28 patients underwent definitive cervical exploration for HPT in the context of MEN 1 at La Timone Hospital, Marseille, France. Another patient referred to us for pancreatic surgery after having received parathyroid surgery elsewhere is included, as the patient has continued follow-up at our unit. Complete follow-up data for recurrence of

HPT were obtained for all of the patients from medical records within the departments of surgery and endocrinology (since departments independently keep records), by contacting the initial referring physician where necessary, and by telephone interviews with patients and their relatives.

The diagnosis of HPT in the presence of MEN 1 was reviewed in all of the cases (Table 1). The range of preoperative total calcium levels for patients was 2.57 to 3.30 mmol/L, with associated inappropriate elevated levels of parathyroid hormone (PTH) (range, 66–207 pg/mL [6.9–21.8 pmol/L]). All of the patients underwent preoperative and postoperative vocal cord inspection.

In this article, SP is defined as identification of 4 parathyroids, excising at least 3 glands, and leaving a remnant the size of a normal parathyroid in the neck (approximately 50 mg). Efforts were made to exclude supernumerary glands and rests of parathyroid tissue by the resection of fatty tissue from the central neck compartment and thymectomy in all of the patients.

Total parathyroidectomy with autotransplantation is the resection of at least 4 glands combined with transplantation of 10 to 20 1-mm³ pieces of parathyroid tissue into separate pockets in the forearm.¹⁰ This was combined with efforts to exclude supernumerary glands and thymectomy.

Less-than-subtotal parathyroidectomy (LSP) is defined as the resection of 1 or 2 pathological glands in the presence of 2 normal glands without thymectomy.

Table 2. Details of Surgical Procedures

| Surgical Procedure | Patients, No. | Male, No./Female, No. | Age, Mean (Range), y | Follow-up, Mean (Range), mo | Patients With Temporary Hypocalcemia, No. (%) | Patients With Permanent Hypocalcemia, No. (%) |
|-----------------------------|---------------|-----------------------|----------------------|-----------------------------|---|---|
| SP | 21 | 7/14 | 40.6 (18-69) | 61.6 (8-192) | 12 (57) | 2 (10) |
| TP with autotransplantation | 4 | 0/4 | 44.5 (36-58) | 167.0 (18-226) | 4 (100) | 1 (25) |
| LSP | 4 | 0/4 | 48.3 (36-57) | 151.5 (49-285) | 0 | 0 |
| Total | 29 | 7/22 | 42.4 (18-69) | 88.5 (8-285) | NA | NA |

Abbreviations: LSP, less-than-subtotal parathyroidectomy; NA, not applicable; SP, subtotal parathyroidectomy; TP, total parathyroidectomy.

Persistent HPT occurs within 6 months of surgery, and recurrent HPT is that occurring more than 6 months following surgery.

RESULTS

Twenty-nine patients (22 female, 7 male; mean age, 42.2 years) were treated surgically between November 1974 and April 2002. Twenty-seven patients underwent primary surgery for HPT in MEN 1. The other 2 patients underwent a second definitive procedure for persistent HPT after having previously undergone surgery elsewhere and are included in the analysis according to the second procedure (1 SP case and 1 TP with autotransplantation case). Twenty-four patients (83%) (Table 1) fulfilled consensus criteria¹¹ for MEN 1 genetic testing owing to the presence of 2 or more main MEN 1–related tumors, and another 3 of 5 patients with a family history of MEN 1 who did not meet the main criteria were suitable for MEN 1 genetic testing on the basis of having multiple parathyroid tumors and being younger than 30 years (27 patients [93%] overall). Mean follow-up was 88.5 months (range, 8–285 months) for all of the patients whereas the mean follow-up for patients with SP was shorter (61.6 months), as this is our current technique and 3 patients in this group who were treated early in our experience have died. Hyperparathyroidism was the first presenting feature of MEN 1 or was found to be present at the time of the first appearance with another feature in 14 (48%) of the patients. Twenty-four patients have other features of MEN 1, including 12 pancreatic lesions, 17 pituitary lesions, and 3 adrenal lesions, whereas 5 patients have only a family history of MEN 1 (1 patient treated in the early 1990s has died and 1 has a confirmed *MEN1* mutation; 3 of the patients were younger than 30 years).

Twenty-one patients received SP, 4 received TP with autotransplantation, and 4 received LSP. No patients had persistent HPT following surgery, and there were no recurrent laryngeal nerve palsies. Twelve (57%) of the patients with SP developed temporary hypocalcemia requiring treatment whereas 2 (10%) of those with SP have permanent hypocalcemia requiring long-term calcium and α -calcitriol supplementation, including the patient undergoing SP as the second procedure for persistent HPT. All 4 of the patients with TP with autotransplantation developed temporary hypocalcemia, and 1 patient has permanent hypocalcemia. No patient with LSP had hypocalcemia (Table 2).

Twenty-six patients (90%) had enlargement of 2 to 5 parathyroids (25 [88%] had more than 2 enlarged), including the patients with only a family history of MEN 1. The histology report was available for 101 parathyroids excised or biopsied, and it showed that 77 patients had hyperplasia, 4 had adenoma, and 20 were normal. One patient with 2 macroscopically enlarged glands had LSP whereas the remaining 25 patients had SP or TP with autotransplantation. Two patients (7%) had a single adenoma at neck exploration, confirmed histologically with evidence of a capsule and a rim of normal parathyroid tissue. Both patients underwent LSP, with biopsy of 2 normal parathyroids. A supernumerary gland was found in 1 patient at first neck exploration and was responsible for recurrence in 1 patient (ie, 2 patients [7%] had supernumerary glands).

Cryopreservation of parathyroid tissue was performed in 5 patients treated between November 1994 and October 1997, but this has not been performed since. Cryopreserved tissue has not subsequently been used.

Four patients died during follow-up (3 patients with SP and 1 with TP with autotransplantation). Two deaths were from MEN 1–related disease (1 pancreas and 1 pancreas and pituitary), 1 death was from breast cancer, and 1 death was cardiac related.

Four patients (14% overall and 43% of those with >10 years of follow-up [Figure]) developed recurrent HPT, including 1 with SP at 57 months, 2 with TP with autotransplantation at 180 and 197 months, and 1 with LSP at 164 months. Three patients have undergone further surgery that resulted in the reversal of hypercalcemia (Table 3).

COMMENT

Controversy remains as to the best surgical approach to HPT in MEN 1. This article is primarily concerned with the results of SP in this group of patients. The small numbers of patients undergoing TP with autotransplantation and LSP (early in our experience) are included for completeness with regard to recurrence rates following surgery.

The diagnosis of MEN 1 may be known or suspected preoperatively with an accurate patient history. However, surgeons need a high index of suspicion when unexpected multiglandular disease is found in patients with primary hyperparathyroidism, and they should consider the possibility of MEN 1, especially in young patients, if inadequate surgery is to be avoided.

Total parathyroidectomy with autotransplantation has been recommended on the basis that it will reduce the incidence of cervical reexploration. The function of autografted tissue to the forearm can be assessed by investigations such as the Casanova test,⁸ and recurrence in the graft can be treated with excision under local anesthesia. However, some disadvantages are that patients undergoing TP with autotransplantation are likely to have hypocalcemia that can be severe^{5,12} before grafted tissue functions, the number of potential sites of recurrence is increased, cervical recurrence is not eliminated, the determination of the site of recurrence is not always straightforward, and determining the volume of grafted tissue to excise is not always easy. Based on our experience of TP with autotransplantation in secondary HPT⁹ in which autotransplantation did not simplify the treatment of recurrent disease, SP remains the procedure of choice for treating MEN 1 (**Table 4**).

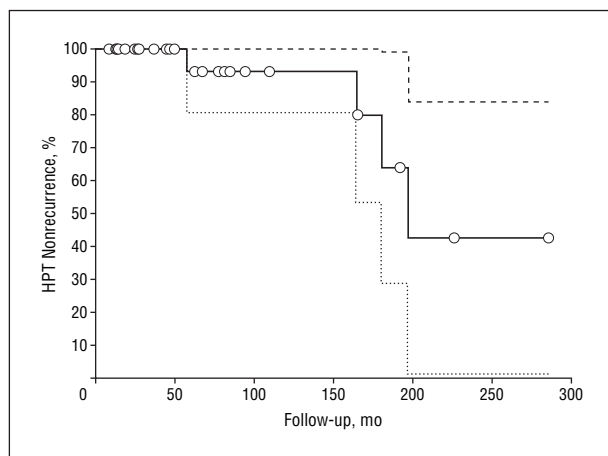


Figure. Recurrence of hyperparathyroidism (HPT) as analyzed by the Kaplan-Meier method. Dashed line indicates upper 95% confidence limit; dotted line, lower 95% confidence limit.

Subtotal parathyroidectomy is an imprecise term that has been used to include varying degrees of parathyroid resection with or without thymectomy,^{5-7,13-15} and variable results have been described. In a review of patients with MEN 1 who were treated in France and Belgium, Goudet et al¹⁶ demonstrated that 60% of 245 patients with HPT underwent surgical treatment. As the percentage of patients treated with adequate SP increased, so did the rate of correction of hypercalcemia. Nonetheless, only 27 (51%) of 53 patients treated since 1991 underwent a true SP, resulting in a persistence of hypercalcemia in 10 (19%) of the patients and in long-term hypocalcemia in 8 (15%).

As defined in this study, there should be no difference in outcome in terms of persistent or recurrent hypercalcemia between SP and TP with autotransplantation, as both procedures involve the controlled excision of parathyroid tissue from the neck and differ only in the site of the parathyroid remnant. We include thymectomy and excision of fatty tissue in the central compartment as part of the procedure to eliminate rests of parathyroid tissue.¹⁷ In preparing the parathyroid remnant in the neck, the most normal-looking parathyroid is selected. It is important that the remnant is well vascularized, and it should therefore be prepared prior to resecting the remaining glands so that an alternative gland can be selected should it become ischemic. The remnant is then marked with a nonabsorbable suture or clip and is attached to the thyroid capsule away from the recurrent laryngeal nerve.

We have not identified a large number of adenomas in patients with MEN 1. Seventy-seven (76%) of the parathyroids excised were described as showing evidence of hyperplasia on the histology reports. The small number of parathyroids described as adenomas demonstrated typical features of a capsule and a rim of normal parathyroid tissue.

Hypocalcemia is less frequent following SP (hypocal-

Table 3. Recurrence of Hyperparathyroidism

| Patient | Surgical Procedure | Time of Recurrence, mo | Reoperation | Findings | Hypocalcemia |
|---------|--------------------|------------------------|-------------|------------------------------|--------------|
| 13 | SP | 57 | Yes | Cervical ectopic fifth gland | Yes |
| 4 | TP | 197 | Yes | Arm graft | No |
| 6 | TP | 180 | No | NA | NA |
| 9 | LSP | 164 | Yes | Cervical left lower | No |

Abbreviations: LSP, less-than-subtotal parathyroidectomy; NA, not applicable; SP, subtotal parathyroidectomy; TP, total parathyroidectomy.

Table 4. Suggested Advantages and Disadvantages of Total and Subtotal Parathyroidectomy

| Surgical Procedure | Advantages | Disadvantages |
|----------------------------|---|--|
| Total parathyroidectomy | <ul style="list-style-type: none"> Reduced recurrence in neck Easier reoperation on graft Local anesthetic surgery on graft Less recurrent laryngeal nerve injury in reoperation | <ul style="list-style-type: none"> Increased sites for recurrence Localization of recurrence more complex Determination of quantity of graft tissue to excise Increased hypocalcemia |
| Subtotal parathyroidectomy | <ul style="list-style-type: none"> Site of remnant in neck known No increased sites for recurrence Localization of recurrence less complex Neck surgery not more difficult Less hypocalcemia | <ul style="list-style-type: none"> Reoperative neck surgery likely Increased recurrent laryngeal nerve injury in reoperation |

cemia was temporary in 12 [57%] of the cases and permanent in 2 [10%] in our series), and it is usually less severe in SP than in TP with autotransplantation.^{5,12} In recurrent disease, the site of the neck remnant is known, and distinguishing cervical from autograft recurrence is unnecessary. Cervical reexploration can be safely performed and can be necessary following both TP with autotransplantation and SP. In a series of 94 reoperations¹⁸ for persistent and recurrent HPT in MEN 1, neck exploration resulted in normocalcemia in 58 (91%) of 64 patients, with recurrent laryngeal nerve injury in 2 patients (2%), whereas autograft removal resulted in normocalcemia in 58% of 9 patients receiving 12 procedures.

There is clearly a small, select group of patients with uniglandular disease^{6,15} (2 patients [7%] in our series) in whom lesser surgery can be successfully performed, although this may not facilitate future reoperative surgery for recurrent disease, and careful patient selection is required to avoid persistent hypercalcemia. Kraimps et al⁶ excised all of the parathyroid tissue from the side of the neck with the adenoma and marked the 2 normal-looking glands on the contralateral side to facilitate future reoperative surgery.

Storage of parathyroid tissue using cryopreservation can be performed as insurance against future hypocalcemia and is especially advisable in reoperative surgery. However, the cost and practicalities of storage of the tissue may not facilitate this option, and stored tissue may not function on the rare occasion when used.⁷ Cryopreservation of parathyroid tissue was performed in 5 patients of our series, but this tissue was not subsequently used.

Some studies^{7,19} have described the usefulness of intraoperative PTH measurements in assessing the completeness of surgical excision. We did not use intraoperative PTH measurements for first-time surgery in this group of patients, as all of the glands were identified during open surgery. A significant false positive rate^{20,21} for intraoperative PTH measurements has been reported in patients with multiglandular disease, and the percentage fall of intraoperative PTH measurements corresponding with successful surgery is uncertain.²² There is probably a role for intraoperative PTH measurement in reoperative surgery.¹⁸

A high index of suspicion for MEN 1 is required when assessing patients with HPT, and surgeons should consider MEN 1 when unsuspected multiglandular disease is discovered in young patients. Overall, recurrent HPT occurs many years following successful initial surgery (median, 14.3 years) and occurred in 7 (43%) of those patients with more than 10 years of follow-up in this series. The time to the development of recurrent HPT is probably not related to the initial extent of surgery.^{5,15} Surgical treatment should avoid persistent HPT while minimizing the risk of permanent hypocalcemia, and most importantly, it should facilitate future surgery for recurrent HPT, which many patients will develop on long-term follow-up. When correctly performed, an SP fulfills these objectives.

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Correspondence: Johnathan G. H. Hubbard, MD, FRCS, Department of General and Endocrine Surgery, First Floor North Wing, St Thomas' Hospital, Lambeth Palace Rd, London SE1 7EH, England (johnathan.hubbard@gstt.nhs.uk).

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