

Minimally Invasive Open Parathyroidectomy in an Endemic Goiter Area

A Prospective Study

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Hypothesis: Single-gland disease identified by preoperative localization studies in combination with rapid intraoperative parathyroid hormone monitoring seems to allow a limited exploration of the neck in sporadic primary hyperparathyroidism. Minimally invasive open parathyroidectomy by lateral approach (oMIP) in sporadic primary hyperparathyroidism seems feasible in an endemic goiter region.

Design: One hundred consecutive patients with sporadic primary hyperparathyroidism underwent preoperative double-phase technetium Tc 99m sestamibi scanning with single-photon emission computed tomography and high-resolution ultrasonography with color Doppler imaging of the cervical region. All patients were operated on with the use of quick parathyroid hormone assay to confirm the surgical success "on-line." Patients with localized single-gland disease, irrespective of additional ipsilateral thyroid disease requiring surgery, were selected for oMIP. Success of the preoperative localization studies, postoperative (at least 6 months) serum cal-

cium levels, and operating time were analyzed.

Setting: University hospital, section of endocrine surgery.

Results: Of 100 patients, 83 (83%) were considered suitable for oMIP. In 69 patients, oMIP was finished successfully. Nine of these had had previous neck surgery, and another 24 underwent additional ipsilateral thyroid resection. Permanent normocalcemia was achieved in 67 (97.1%) of 69 patients and 98 (98%) of 100 patients.

Conclusion: The oMIP in combination with quick parathyroid hormone assay may become the treatment of choice for sporadic primary hyperparathyroidism in an endemic goiter region in centers with high experience in thyroid and parathyroid surgery. It allows treatment of concomitant ipsilateral thyroid disease and is feasible in reoperations.

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SURGERY IS the treatment of choice for most patients with biochemically verified primary hyperparathyroidism (PHPT).^{1,2} If performed by an experienced surgeon, the long-term cure rate for initial bilateral cervical exploration for benign nonfamilial disease is about 99%, with an operative morbidity of less than 1%.³

Despite these excellent results, surgeons continue to explore new ways to treat patients with PHPT in the hope of improving cosmesis, shortening hospital stay, hastening the return to work, and reducing postoperative pain.

Minimally invasive explorations of the parathyroid glands include endoscopic methods,^{4,6} video-assisted techniques,^{7,8} and open "targeted" unilateral explorations through the typical transverse Kocher incision⁹ or open targeted direct explorations through an atypical incision in case of a preoperatively localized adenoma.^{10,11}

The aim of this prospective study was to evaluate the feasibility of minimally in-

vasive open parathyroidectomy (oMIP) in an endemic goiter region through a short paramedian incision, using a lateral approach in sporadic PHPT in combination with rapid parathyroid hormone (PTH) monitoring.

RESULTS

In 91 (91%) of 100 patients, PHPT was caused by SGD and in 9 patients by multiple-gland disease (MGD) (double adenoma, n=5; sporadic primary parathyroid hyperplasia, n=4).

The sestamibi scan was true positive in 76 patients, as was US in 72 (**Table 1**). The combination¹³ of preoperative sestamibi and US scanning correctly identified (true positive) 82 (90%) of 91 patients with SGD. Neither sestamibi nor US scanning was able to predict the exact number and localization of diseased glands in the case of MGD.

Ultrasound demonstrated nodules larger than 1 cm in 1 thyroid lobe in 33 patients and in both lobes in 19 patients.

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PATIENTS AND METHODS

PATIENTS

One hundred consecutive patients with biochemically verified sporadic PHPT were assigned to surgery and included in a prospective surgical protocol. The group consisted of 79 women and 21 men with a mean (\pm SD) age of 63 ± 14 years (range, 16-91 years). The mean (\pm SD) preoperative total serum calcium level was 12.0 ± 1.6 mg/dL (3.0 ± 0.4 mmol/L) (reference range, 8.4 ± 10.4 mg/dL [2.1 - 2.6 mmol/L]), and mean (\pm SD) intact PTH level, 176 ± 158 pg/mL (reference range, 10-60 pg/mL).

By definition,¹² 31 patients (31%) showed classic symptoms of PHPT (renal, bone, and/or gastrointestinal tract manifestations, and hypercalcemic crisis). Sixty-four patients (64%) presented with minimal symptoms (osteopenia, hypertension, and/or symptoms of the "hypercalcemia syndrome"); 5 patients were considered asymptomatic.

All patients underwent preoperative double-phase technetium Tc 99m (^{99m}Tc) sestamibi scanning with single-photon emission computed tomography (SPECT) and high-resolution ultrasonography (US) with color Doppler imaging of the cervical region to localize hyperfunctioning parathyroid glands (sestamibi and US) and to evaluate the morphologic characteristics of the thyroid gland (US).¹³

DOUBLE-PHASE SESTAMIBI SCAN WITH SPECT

Patients were positioned supine with the neck extended. The field of view included the cervical and thoracic regions, with the use of a 128×128 matrix to detect even ectopic parathyroid adenomas. Planar scans were achieved 10 to 15 minutes (early phase) and 120 to 180 minutes (delayed phase) after injection of 13.5 to 16.2 mCi (500-600 MBq) of technetium Tc 99m sestamibi. The SPECT imaging was performed after the delayed phase in axial, sagittal, and coronal planes. The biphasic study was highly suggestive of a parathyroid adenoma if a definite focal uptake was visible on early- and late-phase images. These areas of

increased or separate uptake were best seen after tracer wash-out from the thyroid tissue. In contrast to planar planes, SPECT investigation allowed a correlation with other anatomic structures. All investigations were performed by the same nuclear physician (A.K.) blinded to the result of ultrasonography.

HIGH-RESOLUTION US WITH COLOR DOPPLER IMAGING

The study was performed with the patient supine and the neck extended, with the use of high-resolution transducers (10-13 MHz). The scanned area reached from the submandibular region to the deepest accessible part of the mediastinum. With color Doppler US, the enlarged hyperfunctioning parathyroid glands showed the typical signs of hypervascularization. Thus, parathyroid glands could be distinguished from thyroid nodules. All investigations were done by the same radiologist (C.C.) with a special interest in thyroid and parathyroid disease, who did not know the results of sestamibi scanning with SPECT. The localization and size of the suspected parathyroid adenoma and its relation to the thyroid, esophagus, and carotid artery were plotted. Furthermore, the thyroid gland was scanned for possible concomitant thyroid disease.

A true-positive result was defined as a single abnormal focal accumulation or suspected adenoma on sestamibi or US scanning that corresponded anatomically to a surgically proved parathyroid adenoma. False-positive sestamibi or US scans showed more than 1 abnormal focal accumulation or suspected adenoma, or a single accumulation or suspected adenoma that did not correlate with the site of an excised single adenoma. False-negative sestamibi or US scans showed either no abnormal accumulation or suspected adenoma, or a single focus or suspected adenoma in case of hyperplasia or double adenomas.

QUICK INTRAOPERATIVE PTH ASSAY

A commercially available 2-site antibody chemoluminometric quick PTH (QPTH) assay (Nichols Institute Diagnostic,

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Table 2 shows the correlation between localization studies, adenoma size, and concomitant thyroid disease. In the case of concomitant thyroid disease, the false-positive localized parathyroid adenomas were significantly smaller ($P = .01$; unpaired t test).

As defined above (see "Surgical Strategy" section), 83 (83%) of 100 patients were considered suitable for oMIP; in 69 (83%), oMIP was finished successfully (mean operating time, 45 ± 15 minutes; range, 25-90 minutes). Nine (13%) of these 69 patients had had previous neck surgery (for nodular goiter in 8 and for PHPT in 1). In 24 patients, concomitant, clinically significant ipsilateral thyroid nodular disease was treated by ipsilateral hemithyroidectomy (**Table 3**). In 12 (17%) of 69 patients in the oMIP group, the maximal diameter of the removed adenoma was larger than 30 mm.

Histologic examination showed mild or severe multiple nodular goiter in all patients and an additional

papillary thyroid carcinoma in 4 (stage pT1a, $n=3$; stage pT2a, $n=1$).

In 14 (17%) of the 83 patients who underwent oMIP, a conversion to BNE was necessary (mean operating time, 130 ± 27 minutes; range, 85-170 minutes). Reasons for this were MGD in 5 patients and false-positive localized SGD in 7 patients. In 2 other patients, conversion was necessary because of dissection problems: in 1 patient, the recurrent laryngeal nerve was split into 2 branches and stretched over the parathyroid adenoma. In the other patient, an extremely firm tumor, clustered with the thyroid gland, was suggestive of a parathyroid carcinoma.

Although localized SGD was suspected in 16 of the 17 patients who were not candidates for oMIP, a BNE was chosen from the beginning (mean operating time, 107 ± 21 minutes; range, 65-150 minutes) because of extended bilateral ($n=11$) or contralateral ($n=5$) thyroid disease (Table 3). The final histologic report showed severe multiple nodular goi-

nostic, San Juan Capistrano, Calif) was used in all patients to monitor PTH levels during surgery, as described by Irvin and Deriso.¹⁴

Peripheral-blood samples were taken at the beginning of the operation, at the time of parathyroidectomy, and 5, 10, and 15 minutes after removal of the parathyroid gland(s).

A greater than 50% decline in PTH level 10 minutes after parathyroidectomy confirmed the surgical success. If there was no appropriate decline in PTH concentration, the operation was converted to a standard bilateral neck exploration (BNE).

SURGICAL STRATEGY

Patients with localized single-gland disease (SGD), irrespective of additional ipsilateral thyroid disease, were selected for oMIP. According to our surgical protocol,¹³ oMIP was performed on the side predicted by sestamibi scanning, irrespective of US localization. In case of a negative sestamibi scan, oMIP was performed on the side of positive US (**Figure 1**). Previous neck surgery was not a contraindication for oMIP.

Patients with negative sestamibi and US scans, and/or contralateral and/or bilateral clinically significant thyroid disease requiring surgery, were selected for BNE (**Figure 1**).

All operations were performed by the same experienced parathyroid surgeon (B.N.), with the use of magnifying glasses ($\times 3$) to get a better view of the delicate structures of the explored region, allowing meticulous preparation. A bipolar forceps for coagulation was used to avoid any damage to adjacent structures. The recurrent laryngeal nerve was identified in all patients, irrespective of the surgical technique.

Patients were in a supine position with extended neck. Of the 100 operations, 98 were performed with the patient under general anesthesia and 2 oMIPs used local anesthesia with a cervical block technique.¹⁵

The oMIPs were performed through a 15- to 25-mm (mean, 20-mm) transverse paramedian incision at the lateral edge of a standard deep Kocher incision (**Figure 2**). The surgical approach used resembles that in reoperations

for (para)thyroid disease ("lateral approach"),^{16,17} minimizing the amount of dissection necessary (**Figure 2**). Slight lateral retraction of the sternocleidomastoid muscle and medial retraction of the strap muscles make access to the tracheoesophageal groove possible (**Figure 3**). This allows visualization of the localized enlarged gland(s) and enables the mobilization of the thyroid lobe, also permitting treatment of ipsilateral thyroid disease if indicated. Concomitant thyroid surgery was performed if US demonstrated clinically evident nodule(s) larger than 1 cm or if intraoperative thyroid gland palpation disclosed areas suggestive of disease.

Lower parathyroid adenomas did not require mobilization of the thyroid lobe. In case of descended upper (ie, paraesophageal) parathyroid adenomas or concomitant thyroid disease, we started the operation with mobilization of the upper thyroid pole, followed by identification of the recurrent laryngeal nerve and removal of the parathyroid adenoma.

In this series, we did not have to divide the strap muscles; nevertheless, in the presence of a large thyroid lobe, lateral incision of the strap muscles makes mobilization of the thyroid lobe and visualization of parathyroid glands easier.

For BNE, a 40- to 50-mm standard Kocher incision (mean, 48 mm) was followed by division of the platysma, with preservation of the underlying veins. Incision of the median raphe, lateralization of the strap muscles, and mobilization of the thyroid gland exposed the tracheoesophageal groove.

If the QPTH assay did not show the appropriate decline in serum PTH concentration, the oMIP approach was changed to a BNE (**Figure 1**). To achieve this, the incision was simply extended to the other side of the neck (standard Kocher incision).

Total calcium levels were determined in all patients postoperatively at 1, 4, and 7 days; 6 weeks; and 6 months. Mean (\pm SD) follow-up was 12 ± 5 months (range, 6-22 months). By definition, all patients with normal or subnormal calcium levels were cured. In case of elevated calcium levels, a second blood specimen including intact PTH was drawn to exclude persistent or recurrent disease.

ter in all 16 patients and an additional papillary microcarcinoma in 2 (stage pT1a in both). In the remaining patient, sestamibi scanning and US predicted a double adenoma. At BNE, a 4-gland hyperplasia was detected.

Operating time was significantly shorter for the oMIP group than for the conversion and BNE groups ($P < .01$, unpaired *t* test; **Table 3**). The size of the glands resected was nearly the same in all 3 groups (**Table 3**).

Permanent normocalcemia confirmed the surgical success in 67 (97%) of 69 patients who underwent oMIP and in 98 of 100 patients total. There were no complications in the oMIP and BNE groups. One of 14 patients in the conversion group needed revision because of a hematoma. There was no temporary or permanent recurrent laryngeal nerve palsy.

In 2 patients, oMIP did not succeed. In the first patient, we misinterpreted the QPTH assay and finished the dissection after removal of an enlarged paraesophageal para-

thyroid gland ($18 \times 15 \times 8$ mm), localized on the same side by sestamibi scanning and US. The QPTH assay did not show a 50% decline of PTH level at 10 minutes, although it dropped into the normal range (**Figure 4**). The patient had elevated calcium and intact PTH levels on the first postoperative day, indicating persistent PHPT due to MGD.

At reoperation on the second postoperative day, a second adenoma ($20 \times 9 \times 5$ mm) on the contralateral upper position was found. This time, QPTH assay showed the appropriate decrease of PTH level (**Figure 4**).

In the second patient, preoperative sestamibi scanning and US were suggestive of a single adenoma at the left lower position. A seemingly uneventful oMIP procedure was performed by removing an adenoma ($15 \times 10 \times 3$ mm) in the left thyrothymic ligament, resulting in a typical 50% decline in PTH level (**Figure 5**). Blood investigations on postoperative days 1, 4, and 7 showed values within the reference range for total serum calcium (9.9, 9.6, and 9.7

mg/dL [2.47, 2.41, and 2.42 mmol/L, respectively]) and intact PTH levels (48.4, 47.3, and 46.5 pg/mL, respectively). Six weeks after operation, the patient was hypercalcemic

again (calcium level, 11.2 mg/dL [2.8 mmol/L]) and had a “high-normal” intact PTH value (52 pg/mL). Several blood samples confirmed the diagnosis of persistent PHPT. A sestamibi scan performed 6 months later was suggestive of a second, right lower parathyroid adenoma. At reoperation, a second parathyroid adenoma (14 × 10 × 5 mm) was found in the right thyrothyroidic ligament. The PTH level again showed the typical 50% decline at 10 minutes (Figure 5).

This is our only case in which QPTH failed to predict MGD. Obviously, the second enlarged gland was suppressed at the time of the first exploration (possibly “sleeping hyperfunctioning parathyroid tissue”) and started secreting PTH afterward. Permanent normocalcemia was achieved in both patients by the second exploration.

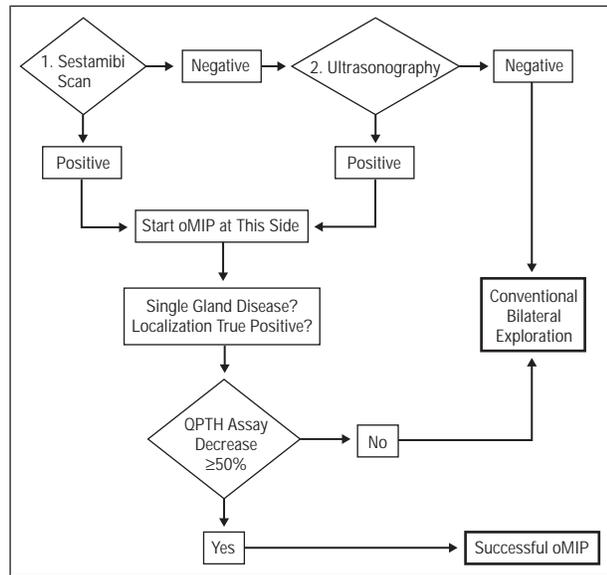


Figure 1. Algorithm for the use of minimally invasive open parathyroidectomy (oMIP), with preoperative technetium Tc 99m sestamibi and ultrasound scanning. QPTH indicates quick parathyroid hormone assay.

COMMENT

For 70 years, BNE with visualization of at least 4 parathyroid glands and resection of all macroscopically diseased glands was accepted as the gold standard in the surgical therapy for PHPT.^{3,18} Attempts at unilateral neck exploration, to reduce surgical trauma and morbidity, were hampered by the difficult intraoperative morphologic and histologic differentiation between SGD and MGD.^{19,20} Preoperative localization studies were not helpful in solving these intraoperative problems.^{21,22}

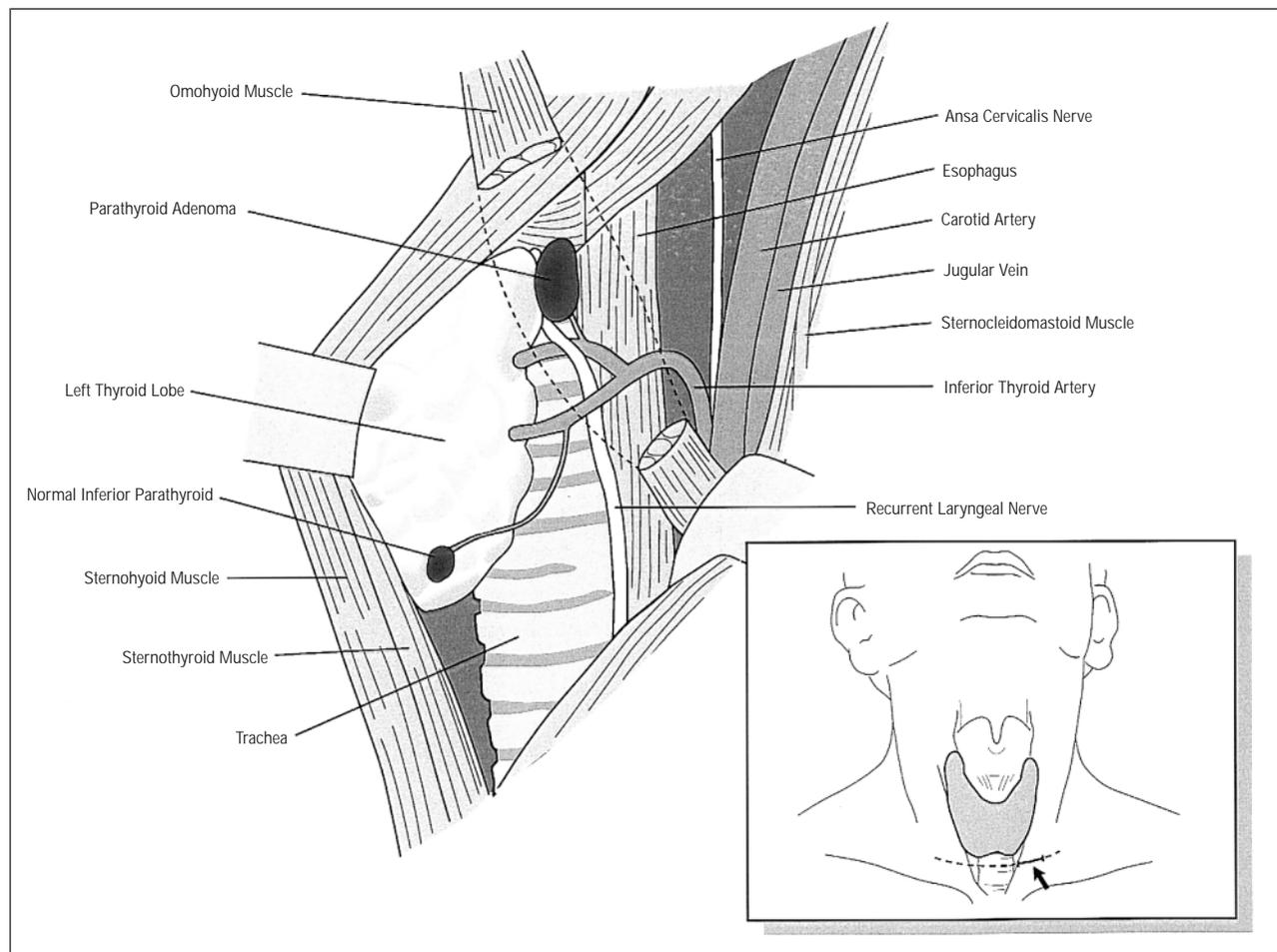


Figure 2. The lateral approach.

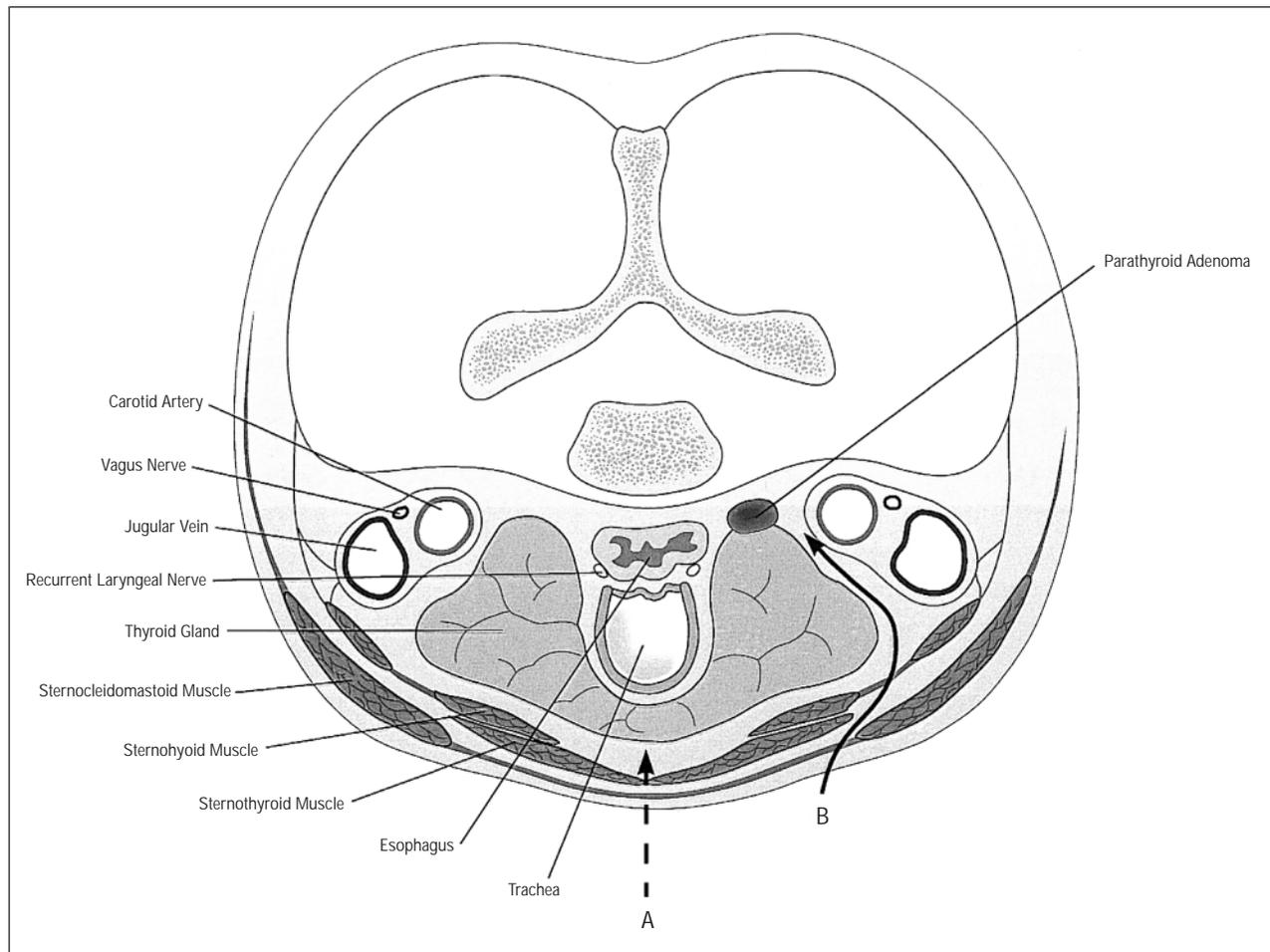


Figure 3. Classic and lateral approaches. A indicates the route for bilateral neck exploration; B, the route for lateral approach.

Table 1. Results of Sestamibi and US Scanning in 100 Patients*

Result	Sestamibi	US	Sestamibi + US†
True positive, No.	76	72	82
False positive, No.	8	15	10
False negative, No.	16	13	8
Sensitivity, %	83	85	91
PPV, %	90	83	89

*US indicates ultrasound; PPV, positive predictive value. Sestamibi was given as technetium Tc 99m sestamibi.

†See Figure 1.

The introduction of the sestamibi scan²³ and the development of the QPTH assay²⁴ were the basis for the development of minimally invasive parathyroid exploration.⁹ Less postoperative distress and better cosmetic results are generally postulated as the main advantages of minimally invasive surgical techniques.²⁵

Minimally invasive open exploration of the parathyroid glands ensures these advantages in patients with biochemically proved sporadic PHPT and localized SGD, with the use of a short paramedian incision (mean, 20 mm) in the supraclavicular fossa on the anterior edge of the sternocleidomastoid muscle and a lateral approach.¹⁷ Smit et al²⁶ reported similar good results, show-

Table 2. Correlation of Localization Studies, Adenoma Size, and Concomitant Thyroid Disease*

	Localization			
	Conversion Group (False Positive)		oMIP Group (True Positive)	
	No. (%) (n = 7)	Mean Adenoma Size, mm	No. (%) (n = 67)	Mean Adenoma Size, mm
Concomitant thyroid disease	6 (86)	12.8†	24 (36)	22.1†
No concomitant thyroid disease	1 (14)	19.0	43 (64)	20.8

*oMIP indicates minimally invasive open parathyroidectomy.

†P = .01, unpaired *t* test.

ing an effective alternative to BNE in selected patients. Additional intraoperative localization techniques, such as US²⁷ and radioisotope scanning,¹⁰ and endoscopic instruments^{8,11,28} are not necessary.

In this prospective study, 83 (83%) of 100 patients were considered suitable for oMIP based on sestamibi and US scanning. Neither concomitant ipsilateral thyroid disease nor previous neck surgery was a contraindication for oMIP. In a literature review,^{6,8,28,29} only 98 (36%) of 271

Table 3. Morphologic Features in 100 Patients With Biochemically Proved Primary Hyperparathyroidism*

	oMIP (n = 69)	Conversion (n = 14)	BNE (n = 17)
Single-gland disease, No.	67	9	15
Double adenoma, No.	2†	2	1
Hyperplasia, No.	0	3	1
Previous neck surgery, No.	9	0	1
Concomitant thyroid disease, No.	24	12	16
Mean gland size, mm	22 × 13 × 7	23 × 13 × 8	22 × 14 × 7
Mean ± SD operating time, min	45 ± 15	130 ± 27‡	107 ± 21‡

*oMIP indicates minimally invasive open parathyroidectomy; BNE, standard bilateral neck exploration.

†Two failures of oMIP: see the "Results" section.

‡ $P < .01$, unpaired t test.

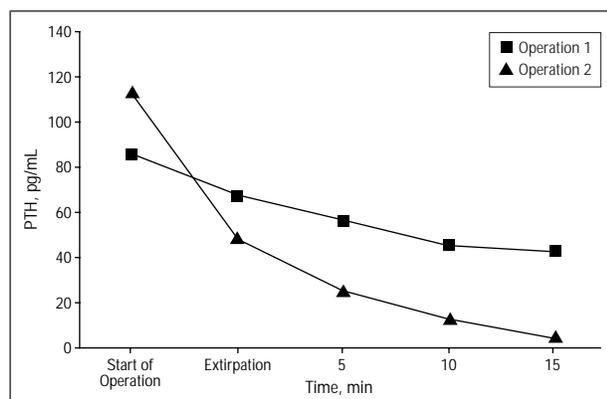


Figure 4. Parathyroid hormone (PTH) levels during surgery demonstrating a missed double adenoma.

consecutive patients were considered suitable for video-assisted parathyroidectomy. In contrast to oMIP, evidence of coexisting nodular thyroid disease and previous neck exploration are contraindications for endoscopic or video-assisted parathyroidectomy.^{28,30}

Because of iodine deficiency, salt has been supplemented with iodine (10 mg of potassium iodine per kilogram of salt) by law since 1963 in Austria, and the concentration was increased to 20 mg of potassium iodine per kilogram of salt in 1990.³¹ Nevertheless, iodine deficiency is still present in a considerable portion of the Austrian population (approximately 40% of persons from a rural region and 30% from Vienna), resulting in iodine deficiency diseases such as endemic goiter.³² In other endemic goiter regions, 11% to 14% of all patients had previous neck explorations because of goiter before sporadic PHPT was diagnosed.³³⁻³⁶ Another 30% to 78% showed coexisting nodular thyroid disease at the time of diagnosis.³³⁻³⁶

Preoperative US documented unilateral or bilateral thyroid nodules in 52 (52%) of the 100 consecutive patients enrolled in this study; 10 of them had had previous neck exploration. If selection criteria for endoscopic or video-assisted parathyroidectomy were applied, only 43 patients (43%) would have been suitable for an endoscopic technique. However, 9 patients who had had previous neck exploration and 24 patients with concomitant thyroid disease successfully underwent oMIP. The

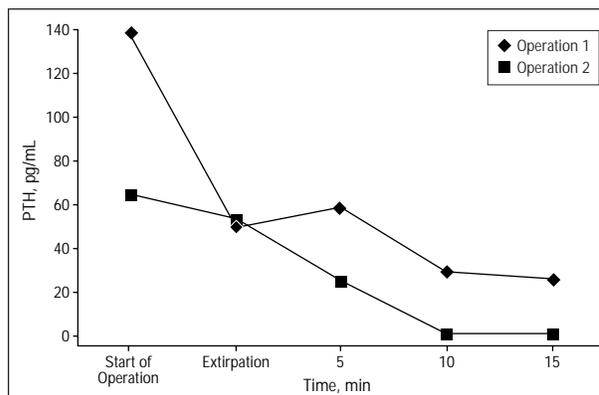


Figure 5. Parathyroid hormone (PTH) levels during surgery demonstrating a missed "sleeping adenoma."

ability to treat ipsilateral clinically significant thyroid disease in oMIP diminishes the potential risk of missing concomitant thyroid carcinomas compared with other minimally invasive approaches in parathyroid surgery.³⁷

Sestamibi scanning combined with US is the most accurate parathyroid localization procedure today.¹³ Sensitivity of sestamibi scanning and US decreases with coexisting nodular changes of the thyroid gland.¹³ Considering that another 5% to 15% of patients with PHPT have MGD, an endoscopic approach can at best succeed in one third of all patients in an endemic goiter region.

By means of preoperative sestamibi scanning and US, the enlarged single gland was identified in 82 (90%) of 91 patients as true positive. Both methods failed to predict MGD in the other 9 patients. These findings are concordant with the literature.³⁸

Surgeons performing a limited approach on the basis of localization studies alone will run the risk of incomplete resection in case of MGD and will therefore record a higher failure rate.³⁹ The QPTH assay acts as a "biochemical frozen section,"^{14,40,41} thus allowing a "functional" diagnosis of MGD. The criterion for the QPTH prediction of postoperative normocalcemia is a drop in the hormone level of more than 50% from the highest preoperative or preexcision value within 10 minutes, after the excision of all hyperfunctioning tissue. With a half-life of the intact PTH of 3.5 to 4 minutes, more than 95% of patients will have this marked drop in their 10-minute postexcision sample.⁴²

In 99 (99%) of 100 patients, QPTH assay reliably confirmed the excision of all hyperfunctioning parathyroid tissue. However, in 1 of these patients, QPTH correctly predicted MGD but was misinterpreted. In the last patient, QPTH confirmed that all hyperfunctioning parathyroid tissue had been excised, but, nevertheless, persisting PHPT occurred. The use of oMIP was feasible in 69 (83%) of 83 patients. Changing the surgical strategy was necessary in 14 (17%) of the 83 patients selected for oMIP because of a wrongly localized (contralateral) single adenoma, double adenoma, or sporadic parathyroid hyperplasia. In the literature, conversion from endoscopic or video-assisted to open bilateral parathyroid exploration is documented in up to 23% of patients.

Because of the limited working space, large parathyroid adenomas complicate or obviate minimally invasive endoscopic or video-assisted parathyroidectomy.²⁸ Of the

69 solitary adenomas in this study, 12 (17%) removed by oMIP were larger than 30 mm in maximum diameter. An argument for the endoscopic or video-assisted approach is the magnification by the camera ($\times 8$), resulting in a meticulous preparation. If magnifying glasses are used, this possible advantage of the endoscopic or video-assisted method is diminished. The advantages of oMIP (and other minimally invasive techniques) will be strengthened by further experience in interpreting reliable preoperative imaging studies and intraoperative QPTH levels.

The overall success rate with oMIP was 97% (normocalcemia in 67 of 69 patients), including patients with unilateral thyroid and previous neck surgery. In none of our patients was persistent hypocalcemia observed. The use of oMIP shortens operating time and avoids the potential risk of increased morbidity from scarring on the unaffected side and prolonged hypocalcemia, which are described in up to 2% of patients undergoing BNE, caused by looking for all glands.³

Compared with BNE, the mean (\pm SD) operating time for video-assisted parathyroidectomy is significantly shorter (70 ± 18 minutes vs 57 ± 15 minutes²⁵). For oMIP compared with BNE or conversion, the operating time for oMIP was significantly shorter: only 45 ± 15 minutes. Minimally invasive open parathyroidectomy may be performed without complications and with a low rate of morbidity with general or local anesthesia on an outpatient basis in centers with substantial experience in parathyroid and thyroid surgery.⁴³

Concerning the costs of oMIP, less anesthesia time is not only beneficial to the patient but also helps to lower overall surgical costs.^{11,44}

Patients with previous neck surgery and/or concomitant ipsilateral thyroid disease can be treated successfully by oMIP. The use of oMIP in combination with QPTH may therefore become the treatment of choice for the majority of patients with sporadic PHPT in an endemic goiter region.

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