



Targeted Parathyroidectomy in the Era of Intraoperative Parathormone Monitoring

William B. Inabnet III, M.D.,¹ Gregory F. Dakin, M.D.,¹ Richard S. Haber, M.D.,² Francesco Rubino, M.D.,¹
Ed J. Diamond, Ph.D.,² Michel Gagner, M.D.¹

¹Department of Surgery, The Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, New York 10029, USA

²Division of Endocrinology, Department of Medicine, The Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, New York 10029, USA

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Abstract. A combination of preoperative localization and intraoperative parathormone (PTH) monitoring permits targeted parathyroidectomy. Multiple approaches have been developed, ranging from unilateral neck exploration (UE) to radio-guided parathyroidectomy (RP) to endoscopic parathyroidectomy (EP). The purpose of this study was to evaluate the efficacy of these approaches in the management of primary hyperparathyroidism. From June 1998 to November 2000 a total of 110 targeted parathyroid operations were performed at a university medical center. All patients underwent technetium-99m-sestamibi scanning, ultrasonography, or both prior to surgery. Intraoperative PTH monitoring was utilized in all cases. Thirty-seven patients underwent UE, 59 underwent RP, and 14 underwent EP. Follow-up ranged from 1 to 24 months. All patients were cured following parathyroidectomy as predicted by a more than 50% reduction of the intraoperative PTH level following removal of all hyper-secreting glands. Altogether, 103 patients had a solitary adenoma (95%), and 1 patient had a parathyroid carcinoma. Six patients (5%) had multigland disease, including four cases of hyperplasia and two patients with a double adenoma. Eighty-three patients (75%) were discharged the day of surgery. The use of preoperative localization and intraoperative PTH monitoring permits a targeted approach to the treatment of primary hyperparathyroidism. Endocrine surgeons should be facile in all minimally invasive parathyroid techniques to individualize the operative approach.

Since the first parathyroidectomy by Felix Mandl in 1925, the principles of parathyroid surgery have experienced a dramatic evolution [1]. In the early history of parathyroid surgery, patients presented late in the disease course with severe bone disease and complications of renal calculi. Conventional bilateral neck exploration was the preferred approach, resulting in a 95% cure rate when performed by an experienced surgeon [2, 3]. The 1960s brought the development of the radioimmunoassay for parathyroid hormone (PTH) and widespread use of the serum chemistry analyzer, both of which resulted in an earlier diagnosis of hyper-

parathyroidism (HPT) [4]. The era of preoperative localization began with ultrasonography during the late 1970s and was soon followed by technetium-thallium scintigraphy [5, 6]. Although most patients harbor a solitary adenoma, bilateral neck exploration remained the standard of care.

The first report of unilateral neck exploration for HPT was by Tibblin et al. in 1982 [7]. In this landmark paper the authors concluded that a unilateral approach reduces the operating time, decreases the risk of complications and early hypocalcemia, and offers more favorable technical conditions for reoperation. With the more recent development of technetium-99m-sestamibi scintigraphy, high-resolution real-time ultrasonography, and the rapid PTH assay, minimally invasive parathyroidectomy has gained widespread acceptance among endocrine surgeons [8–10]. Several targeted approaches have been developed, ranging from unilateral neck exploration under local anesthesia to video-assisted and complete endoscopic techniques [11–13]. The purpose of this study was to evaluate the efficacy of three targeted minimally invasive approaches to the surgical management of primary HPT.

Materials and Methods

Patients

From June 1998 to November 2000 a total of 130 patients with biochemically documented primary HPT were referred for surgery at a single university medical center. Of these patients, 110 were eligible for targeted parathyroidectomy based on successful localization of a solitary enlarged gland with technetium-99m-sestamibi scanning, ultrasonography, or both. The three targeted approaches included unilateral neck exploration ($n = 37$), radio-guided parathyroidectomy ($n = 59$), and endoscopic parathyroidectomy ($n = 14$). The choice of operative approach was based on many factors including patient preference, body habitus, the age and medical condition of the patient, a history of prior neck surgery (i.e., persistent or recurrent HPT), the kinetics of tracer retention (i.e., on technetium-99m-sestamibi scintigraphy, and the size

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Correspondence to: W.B. Inabnet III, M.D., Department of Surgery, Mount Sinai Medical Center, 5 East 98th Street, Box 1259, New York, NY 10029, USA, e-mail: b.inabnet@mountsinai.org

Table 1. Presenting symptoms in patients with primary hyperparathyroidism.

Symptom	No. of patients
Fatigue	57 (52%)
Nephrolithiasis	17 (15%)
Muscle aches	15 (14%)
Nocturia	13 (12%)
Depression	13 (12%)
Osteoporosis	13 (12%)
Polyuria	12 (11%)
Thirst	11 (10%)
Asymptomatic	10 (9%)
Bone/joint pain	6 (5%)
Constipation	3 (3%)
Hypertension	2 (2%)
Memory loss	1 (1%)
Gout	1 (1%)
Psychosis	1 (1%)

and location of the adenoma. Exclusion criteria for targeted parathyroidectomy included the presence of thyroid disease necessitating a bilateral neck exploration, a suspicion of multigland disease [multiple endocrine neoplasia (MEN)-related HPT], and unsuccessful preoperative localization.

The mean age was 59 years (range 12–92 years), and the group included 24 men (22%) and 86 women (78%). A series of 108 patients (98%) presented with sporadic HPT, but 2 patients with non-MEN familial HPT and a solitary enlarged parathyroid gland visualized on preoperative imaging were also included in the analysis. The most common symptom referable to HPT was fatigue, present in 57 patients (52%), followed by kidney stones, muscle aches, and nocturia/polyuria (Table 1). Ten patients (9%) were asymptomatic. The mean preoperative calcium and PTH levels were 11.2 ± 0.88 mg/dl (mean \pm SD) and 181 ± 135 pg/ml, respectively. Technetium-99m-sestamibi scintigraphy was performed in 109 of 110 patients and ultrasonography in 105 of 110 patients.

Overall, nine patients had a history of previous neck surgery, including thyroidectomy in three patients and tracheostomy in two. Four patients had persistent or recurrent HPT, all of whom had undergone their previous operations at another medical center.

Intraoperative PTH Monitoring

Intraoperative PTH monitoring was utilized in all cases. The rapid PTH assay is a commercially available immunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) that uses two polyclonal antibodies directed against the intact PTH peptide. The entire assay cart is portable and can be transferred to the operating room, thereby eliminating specimen transfer time. Blood was preferably collected from an antecubital venous catheter, but often a radial arterial line was inserted to ensure a reliable, timely measurement of peripheral PTH. The total turnaround time from collecting a blood specimen to obtaining a PTH result was 12 minutes. PTH levels were measured at baseline, during manipulation, and at 5, 10, and 30 minutes following parathyroidectomy. If there was a more than 50% reduction from the highest baseline value, the operation was terminated without identifying the remaining parathyroid glands. If there was an

appropriate decrease in PTH levels 5 minutes following parathyroid excision, the later PTH values were obtained in the recovery room. If the PTH levels remained inappropriately elevated following targeted parathyroidectomy, a bilateral neck exploration was performed during the same procedure.

Surgery

Unilateral Neck Exploration. For unilateral neck exploration (UE) the patient is positioned supine with the head extended and the arms retracted downward and tucked at the patient's side. Patients were administered intravenous sedation (midazolam). After standard sterile draping, local anesthesia (1% lidocaine without epinephrine) was injected into the skin and the subcutaneous tissue overlying the affected gland as well as over the ipsilateral sternocleidomastoid muscle. A 2 cm incision was made, preferably in a natural skin crease. The sternocleidomastoid muscle was retracted laterally, and the underlying strap muscles were separated with alternating sharp and blunt dissection. The thyroid lobe was gently mobilized and retracted in an antero-medial direction.

With minimal dissection, the enlarged parathyroid gland was identified and carefully mobilized. If the gland was situated in a deep location, an attempt was made to identify the recurrent laryngeal nerve. Sedation was kept at a minimum so the surgeon (W.B.I.) could monitor the patient's voice. The vascular pedicle to the adenoma was dissected and ligated with a small vascular clip. The incision was closed in two layers with absorbable sutures. Most patients were discharged approximately 2 hours after surgery.

Radio-guided Parathyroidectomy. Only patients with a solid focus on sestamibi scanning were eligible for radio-guided parathyroidectomy (RP) [14]. Approximately 2 hours prior to surgery, patients received 18 to 20 mCi of technetium-99m-sestamibi. In the operating room, a gamma probe (Neoprobe; Johnson and Johnson, Cincinnati, OH, USA) was used to measure radioactivity in the neck. The thyroid isthmus was used to measure background counts, and then the radioactivity was measured in each quadrant of the neck. After injecting local anesthesia in a manner identical to that described for UE, an incision was made at the point of maximal radioactivity in the quadrant of the neck corresponding to the preoperative sestamibi localization. The gamma probe was used to guide the surgical dissection. Once the gland was encountered, it was dissected and removed as described for UE. Most patients were discharged approximately 2 hours following surgery.

Endoscopic Parathyroidectomy. For endoscopic parathyroidectomy the patient was placed in the supine position with the neck in a neutral position. After induction of general endotracheal anesthesia, the neck was prepared and draped in the standard fashion. A 5 mm incision was made in the midline just above the sternal notch and carried sharply through the platysma. A 5 mm trocar was inserted and secured with a purse-string suture. Carbon dioxide was insufflated to 10 mmHg. A 5 mm zero-degree endoscope was used to develop the avascular subplatysmal space with blunt dissection using the tip of the endoscope. Dissection of this plane was concentrated on the side of the localized adenoma. Once enough space had been created, a 30-degree endoscope was used for the remainder of the case. Two additional 2- to 3-mm

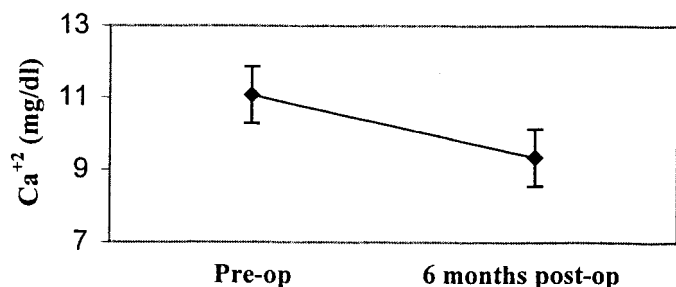


Fig. 1. Serum calcium levels before (Pre-op) and 6 months after (post-op) targeted parathyroidectomy in 47 patients with 6 months of follow-up.

ports were placed in the lateral neck under direct vision. In most cases a lateral approach (lateral to the strap muscles, medial to the carotid artery) was used to gain access to the parathyroid basin. Dissection proceeded until the involved gland was encountered. Unlike UE and RP, the recurrent laryngeal nerve was identified routinely and traced throughout its entire course near the involved gland. The gland was dissected free of surrounding attachments, and the vascular pedicle was ligated with a mini-endoloop. When necessary, the camera was switched to a 3 mm mini-endoscope so a 5 mm clip applier could be used. The gland was placed in a small bag (fashioned from the cut finger of a sterile glove) and removed via the 5 mm trocar site. The trocar sites were closed with Steri-Strips. Most patients were discharged home on the first postoperative day.

Statistics

The single-factor ANOVA test was used to compare results between operative groups.

Results

All patients were cured following parathyroidectomy as predicted by a more than 50% reduction of intraoperative PTH levels following excision of all hypersecreting glands. Three weeks after surgery the mean postoperative calcium and PTH levels were 9.1 ± 0.91 mg/dl and 78.0 ± 51 pg/ml, respectively. Six-month follow-up data were available for 47 patients and revealed mean calcium and PTH levels of 9.3 ± 0.77 mg/dl and 78.2 ± 60 pg/ml, respectively (Fig. 1).

The outcomes of the various targeted approaches are summarized in Table 2. There was no statistical difference in demographic data between each group except for patients undergoing RP, who were older than those undergoing UE or EP ($p < 0.05$). The mean operating times—defined as the time from incision to receipt of the first postexcision PTH result that had decreased more than 50% of baseline—were 57, 62, and 146 minutes for UE, RP, and EP, respectively. Among the patients undergoing UE and RP under local anesthesia, 14 required conversion to general anesthesia for the following reasons: multigland disease necessitating bilateral neck exploration ($n = 3$), inability to locate the targeted gland ($n = 2$), inadequate exposure or intolerance of local anesthesia ($n = 5$), and a deep or ectopic location ($n = 4$). In 20 of 59 patients undergoing RP, the gamma probe provided confusing information to the surgical team or did not function

Table 2. Outcome of targeted approaches for parathyroidectomy.

Parameter	UE	RP	EP
No. of patients	37	59	14
Age (years), mean and range	56 (22–80)	62 (12–92)	51 (21–67)
History of recurrent or persistent HPT	0	4	0
Anesthesia			
Local	15	48	0
General	11	8	14
Conversion from local to general	11	3	N/A
Mean OR time (min)	57	62	146
Median LOS (hours)	2.5	3.0	23
Cure	37/37	59/59	14/14

UE: unilateral neck exploration; RP: radioguided parathyroidectomy; EP: endoscopic parathyroidectomy; OR: operating room; LOS: length of stay; HPT: hyperparathyroidism.

Table 3. Complications of targeted parathyroidectomy.

Complication	UE	RP	EP
Hematoma	1	—	—
Pneumothorax	—	1	—
Pneumonia	—	1	—
Temporary RLN palsy	—	1	—
Traumatic intubation	1	—	—
Death	—	1	—

RLN: recurrent laryngeal nerve.

properly; a UE was successfully completed in each of these patients.

Seventy-five percent of patients were discharged on the day of surgery. The median lengths of stay—defined as the time from the end of surgery to discharge from the hospital—were 2.5 and 3.0 hours for the UE and RP groups, respectively; the median length of stay for the EP group was 23 hours ($p < 0.05$).

There were a total of six complications in the three groups (Table 3). The one death occurred in a patient with multisystem organ failure who developed hypercalcemic crisis necessitating emergent parathyroidectomy. The operation was successfully completed in 25 minutes, but the patient succumbed to her underlying medical problems on the sixth postoperative day.

Final pathology showed a solitary adenoma in 104 patients (95%), with 1 patient having a parathyroid carcinoma. The mean weight of the excised glands was 1283 ± 1276 mg. There were six cases (5%) of multigland disease, including two patients with a double adenoma and four with hyperplasia.

In each case of *multigland disease*, the intraoperative PTH levels failed to decrease appropriately following excision of the targeted gland, and a bilateral neck exploration was performed during the same procedure. Following excision of all hyperfunctioning glands, the intraoperative PTH levels decreased appropriately relative to baseline values ($> 50\%$ baseline). In one patient with a double adenoma undergoing RP, the gamma probe failed to detect the presence of the second hypersecreting gland. Three of the four patients with hyperplasia underwent subtotal parathyroidectomy (one completed endoscopically) with cyropreservation of one of the glands. The other patient with hyperplasia underwent three-gland parathyroid excision because the fourth gland

was not enlarged and the intraoperative PTH values normalized following three-gland parathyroidectomy.

Discussion

The principles of minimally invasive parathyroidectomy include successful preoperative localization of a solitary adenoma, a targeted operative approach that does not disturb the normal parathyroid glands, and intraoperative confirmation of excision of all hypersecreting glands. Each of the approaches utilized in this series—unilateral neck exploration, radio-guided parathyroidectomy, and endoscopic parathyroidectomy—adheres to these principles. The advantages of a targeted approach include the possible use of local anesthesia, decreased operating times, a lower incidence of hypocalcemia, a more favorable cosmetic result, and a quicker recovery [12]. Moreover, if recurrent HPT were to develop in the future, there would be more favorable technical conditions for reoperation and thus a theoretic reduction in the complication rate with surgery for recurrent disease. Although any analysis of patients undergoing targeted parathyroidectomy has selection bias owing to the requirement of successful preoperative localization, numerous studies have demonstrated an equal or superior cure rate compared to that of a conventional bilateral neck exploration [10, 12–15].

Improvement in the sensitivity of parathyroid imaging techniques has undoubtedly played an important role in the feasibility and success of targeted parathyroidectomy. In experienced hands, high-resolution ultrasonography has a sensitivity of 70% to 80%, but the sensitivity of this imaging modality is directly related to the experience of the examiner [16]. Ultrasonography provides important anatomic information to the surgeon, such as the size and depth of a parathyroid adenoma and its relation to the thyroid gland, esophagus, and carotid artery. Moreover, coexisting thyroid abnormalities can be identified, including thyroid nodules and Hashimoto's thyroiditis. This information plays a role not only in selecting patients for targeted parathyroidectomy but also in the choice of operative approach. For example, the presence of thyroiditis is a relative contraindication to endoscopic parathyroidectomy due to increased adherence of the strap muscles to the thyroid gland. The sensitivity of dual-phase sestamibi scanning is slightly superior to that of ultrasonography, ranging from 80% to 90% [17–19]. Sestamibi scanning has the added advantage of evaluating the mediastinum, which cannot be assessed with ultrasonography. These localizing tests provide complementary information, and both influence the choice of targeted parathyroidectomy.

The rapid PTH assay, which has been one of the most important recent advances in parathyroid surgery, plays an integral role in the intraoperative decision-making process during targeted parathyroidectomy. Multiple studies have shown that a more than 50% reduction in baseline PTH values reliably predicts eucalcemia following parathyroidectomy [9, 10, 12, 16]. Most importantly, intraoperative PTH monitoring provides immediate feedback to the surgical team regarding the adequacy of the parathyroid excision [20]. In most cases a solitary adenoma is the cause of primary HPT; and if there is an appropriate decrease in PTH levels, no attempt is made to visualize the remaining parathyroid glands. In the current series, the rapid PTH assay correctly identified each case of multigland disease, including four cases of hyperplasia and two double adenomas. In each of these cases,

bilateral neck exploration and excision of all abnormal glands led to an appropriate decrease in intraoperative PTH levels.

Over the last decade, targeted parathyroidectomy has gained acceptance among most endocrine surgeons. Controversy exists, however, as to which approach is the most efficacious and cost-effective. Unilateral neck exploration has numerous advantages over the other minimally invasive approaches, including the use of local anesthesia, intraoperative voice monitoring, shorter operating times, and same-day discharge [12]. Although endoscopic parathyroidectomy requires general anesthesia and takes longer than the other approaches, it provides the best cosmetic result and allows safe access to deep and ectopic locations, including the mediastinum [11, 21]. Moreover, the magnification afforded by the endoscope provides the best visualization of cervical anatomy, especially the recurrent laryngeal nerve. The results of this study showed absolutely no benefit for the routine use of radio-guidance, a finding supported by the fact that the gamma probe provided confusing information to the surgical team in 30% of cases in which it was used. Other disadvantages of the radio-guided parathyroidectomy include the additional small dose of radiation exposure to the patient and coordinating the administration of the radioisotope with the operating room schedule, especially when several cases are planned for the same day [14]. The use of radio-guidance is recommended only in cases of persistent or recurrent HPT, where the gamma probe may direct the surgeon more precisely to the offending gland, which is often embedded in scar tissue.

Targeted parathyroidectomy requires successful preoperative localization and the availability of intraoperative PTH monitoring. Endocrine surgeons should be skilled in all of the targeted approaches so the operative approach can be individualized.

Résumé. En combinant l'information obtenue en préopératoire sur la localisation des glandes et en peropératoire, à partir du monitoring de la parathormone (PTH), on peut réaliser une parathyroidectomie dite «ciblée». Pour ce faire, on a développé de multiples approches, allant de l'exploration cervicale unilatérale (ECU) à la parathyroidectomie radioguidée (PR) et à la parathyroidectomie laparoscopique (PL). Le but de cette étude a été d'évaluer l'efficacité de ces différentes approches dans la prise en charge de l'hyperparathyroïdie primitive. Entre juin 1998 et novembre 2000, on a réalisé 110 interventions «ciblées» sur la parathyroïde dans un centre médical universitaire. Tous les patients ont eu une scintigraphie au technetium-99m-sestamibi et/ou une échographie avant l'intervention. Le monitoring peropératoire de la PTH a été utilisé dans tous les cas. Trente-sept patients ont eu une ECU, 59, une PR, et 14, une PL. Avec un suivi entre 1 et 24 mois, tous les patients ont été guéris après leur parathyroidectomie comme le laissait prévoir une réduction supérieure à 50% du dosage peropératoire de la PTH après ablation de toutes les glandes hypersécrétantes. Cent trois patients avaient un adénome solitaire (95%) et un patient avait un cancer de la parathyroïde. Six patients (5%) avaient une maladie multiglandulaire, y compris quatre cas d'hyperplasie et deux patients porteurs d'un adénome double. Quarante-trois patients (75%) ont pu quitter l'hôpital le jour de leur intervention. La localisation préopératoire et l'utilisation du monitoring peropératoire de la PTH permettent une approche «ciblée» dans le traitement de l'hyperparathyroïdie primitive. Les chirurgiens endocrines devraient être familiers avec toutes les techniques mini-invasives de la parathyroidectomie afin de pouvoir adapter l'approche opératoire à chaque cas individuel.

Resumen. El diagnóstico de localización preoperatorio y la monitorización intraoperatoria de la hormona paratiroidea (PTH) han permitido alcanzar el objetivo de la paratiroidectomía selectiva, mínimamente invasiva. Se han propuesto con dicha finalidad: desde la exploración unilateral del cuello (UE) a la radioparatiroidectomía guiada

(RP), pasando por la paratiroidectomía endoscópica (EP). El objetivo de este trabajo fue determinar la vía de abordaje idónea para el tratamiento del hiperparatiroidismo primario. Desde junio de 1998 a noviembre de 2000 se realizaron, en nuestro centro, 110 paratiroidectomías. En todos los pacientes se efectuó una gammagrafía con tecnecio-99 m-sestamibi y/o una ecografía preoperatoria. En todos los casos la PTH se monitorizó durante la intervención. 36 pacientes fueron tratados quirúrgicamente mediante UE, 59 con RP y 14 con EP. El seguimiento oscila entre 1–24 meses. Todos los pacientes curaron tras la paratiroidectomía como demostró una reducción superior al 50% de los valores intraoperatorios de la PTH al extirpar la o las glándulas hipersecretoras. 103 pacientes presentaron un adenoma solitario (95%); 1 paciente un carcinoma; 6 enfermos (5%) padecían una enfermedad multiglandular: 4 casos de hiperplasia y 2 de doble adenoma. 83 (75%) de los pacientes fueron dados de alta el día de la operación. Las pruebas diagnósticas preoperatorias y la monitorización de la PTH durante la intervención quirúrgica, permiten un seguro tratamiento curativo del hiperparatiroidismo utilizando cualquier vía de abordaje mínimamente invasiva.

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