IMAGE GUIDED, MINIMALLY INVASIVE ADENOMECTOMY FOR SOLITARY GLAND DISEASE

IN

PRIMARY HYPERPARATHYROIDISM

Pieter Casper Smit

Image guided, minimally invasive adenomectomy for solitary gland disease in primary hyperparathyroidism.
Smit, Pieter Casper.

Utrecht, Universiteit Utrecht, Faculteit Geneeskunde.
Proefschrift Universiteit Utrecht, met een samenvatting in het Nederlands.

ISBN: 90-393-2720-3

Lay-out: Audio Visuele Dienst, UMC Utrecht
Printed by: FEBODRUK BV Enschede
Cover: Tegelvloer met naakt.
Matthijs Röling, 1973

Financial support for publication of this thesis was provided by: ATL Nederland A Philips Medical Systems Company, Chirurgisch Fonds Universitair Medisch Centrum Utrecht, Diagnostic Products Corporation Nederland bv.

IMAGE GUIDED, MINIMALLY INVASIVE ADENOMECTOMY FOR SOLITARY GLAND DISEASE

IN

PRIMARY HYPERPARATHYROIDISM

Minimaal invasieve bijschildklier chirurgie voor solitaire bijschildklier adenomen
bij primaire hyperparathyroïdie
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de Rector Magnificus, Prof. dr W.H. Gispen, ingevolge het besluit van het College voor Promoties in het openbaar te verdedigen op dinsdag 22 mei 2001 des namiddags te 2.30 uur

door

Pieter Casper Smit

Geboren op 18 januari 1968 te Vlissingen

Promotor : Prof. dr Th.J.M.V. van Vroonhoven

Co-promotor : Dr I.H.M. Borel Rinkes

In memory of my mother and father

To C.K. Schoen-Obbink

Contents

A case of persistent hyperparathyroidism after conventional neck exploration: an unexpectedly simple solution to a difficult problem

1

A 57-year-old man was referred to the University Medical Center Utrecht with persistent hypercalcemia after a bilateral neck exploration for primary hyperparathyroidism (pHPT). The operative notes were reviewed and showed that a thorough and systematic procedure had been performed. During the initial exploration a normal superior parathyroid gland had been identified on the right side of the neck; this was left in situ. A second, slightly enlarged, inferior gland at the same side was resected. On the left side of the neck the superior gland was judged to be normal, but notwithstanding all efforts including thymectomy and thyroidotomy, the inferior gland on this side could not be found, whereafter the exploration was discontinued. Persistent hypercalcemia postoperatively indicated that the causative adenoma had not been identified. Upon referral to our hospital the diagnosis pHPT was confirmed biochemically. Since the patient was symptomatic (nephrolithiasis) with elevated serum calcium levels of 2.95 mmol/L (normal range 2.20-2.60) the indication for reoperation was unavoidable. The initial work-up, as usual for reoperative cases in our institution, consisted of Doppler ultrasonography (US), spiral computed tomography (CT), magnetic resonance imaging (MRI), thallium201-technetium-Tc99m pertechnetate scanning (ThTc) and selective venous parathormone (PTH) sampling. Relying upon the information gained at first exploration, the test results were studied with special attention for the left side of the neck and mediastinum. None of the test results showed any evidence of an adenomatous lesion in the mediastinum. Selective venous PTH sampling showed increased levels of PTH at multiple levels on the right side and only one selective high level of PTH on the left side of the neck. Because this was contrary to what we expected, the possibility of a third gland on the right side was considered. The only positive added value of venous PTH sampling was the presumed cervical (and not mediastinal) location of the lesion. MRI did not show any evidence of an adenoma. Ultrasonography was negative except for one lesion ventral to the carotid sheath at the level of the mandibular angle and the hyoid bone on the left side. The location of this 2-cm oval shaped lesion was typical for a lymphnode. However its intense Doppler flowpattern was atypical for the ultrasonographic characteristics of lymphatic tissue. Therefore, we decided to complete the analysis with fine needle aspiration. Microscopy irrefutably proved the nature of the mass: parathyroid tissue. Revision of the CT images revealed an ectopic adenoma at the location indicated by US, which had been missed during the first evaluation (**Figure 1**). Since the lesion was now proven to be the fourth (missing) parathyroid gland we focused on this lesion alone. The operative plan consisted of a local procedure at the indicated site. A small incision was made at the ventral border of the sternocleidomastoid muscle at the level of the hyoid bone. After only a few minutes of exploration a well vascularised, red-brownish, oval shaped lesion (macroscopically a parathyroid adenoma) was found in the direct vicinity of the submandibular gland. Once the lesion was resected the exploration was terminated. Postoperatively, the calcium level had returned to normal on day one. Histological examination of the specimen

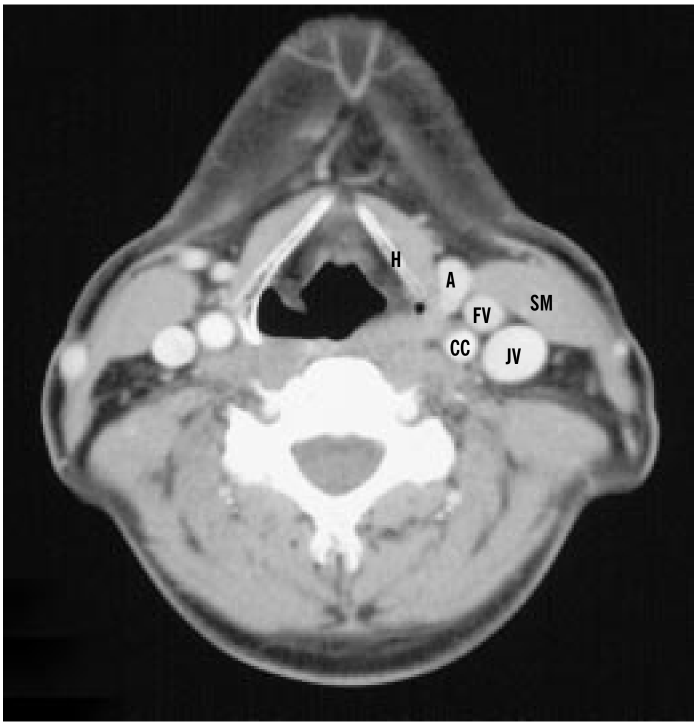


Figure 1 *Cross section image of Computed Tomography showing an adenoma at the level the hyoid bone. Adenoma (A), hyoid bone (H), common carotid artery (CC), internal jugular vein (JV), facial vein (FV), sternocleidomastoid muscle (SM).*

confirmed the diagnosis: parathyroid tissue. Currently, more than 6 years post-resection, the patient is still normocalcemic.

After a thorough and systematic exploration performed by an experienced endocrine surgeon, persistent hyperparathyroidism still cannot be precluded in all patients as is illustrated by this case. These complications in parathyroid surgery are mostly caused by the variability in location of the glands, rather than by the variety in the number of affected glands. The majority of ectopic parathyroids (adenomas), however, can be found in the vicinity of the lower pole of the thyroid and upper part of the thymus. A rule of thumb is that the further the distance from parathyroid to thyroid the lower the frequency of ectopic parathyroid tissue. A parathyroid adenoma located at the level of the hyoid bone, as in the case presented, is extremely rare (<0.1%) [1,2]. This can be explained by the fact that -in contrast to the superior parathyroid gland whose position remains relatively constant- the inferior parathyroid gland travels a long distance during fetal development

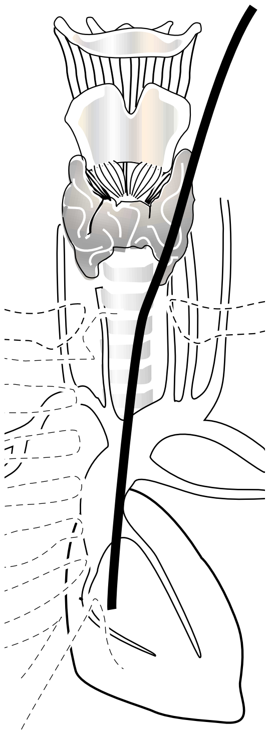


Figure 2 *Descent of the inferior parathyroid gland. The inferior parathyroid gland migrates during fetal life and may end up anywhere along the path of descensus (black line).*

Adapted from Kaplan EL. Thyroid and parathyroid. Chapter 38. Schwartz SI, ed. Principles of Surgery, 5th edition. New York: Mc Graw-Hill, 1989; 1613-1685.

together with the thymus and may thus be found anywhere from the angle of the jaw to the pericardium (**Figure 2**). In a case when the migration of the parathyroid gland is interrupted during development one speaks of a non-descended parathyroid.

The quality and reliability of imaging modalities have improved substantially over the last decade. In this case the missing adenoma was ultimately found on US performed by an experienced, persistent radiologist. All other localizing studies were negative, but for CT. The adenoma was initially overlooked in the CT examination because of its rare ectopic position, rather than its radiological characteristics. The selective venous PTH sampling was inconclusive. With hindsight, the combination of US and CT convincingly localized the adenoma, even in a most surprising position.

In this case the transition from failure to success was realized by a minimally invasive, local procedure relying upon state-of-the-art imaging technology and a direct approach to the lesion. Based on the success of this relatively simple and quick procedure we wondered whether such a direct, minimally invasive strategy could be utilized for the 'standard' case of pHPT as well. We speculated that it might serve as an alternative for the conventional neck exploration. The results of this speculation are reported in this thesis.

References

1 Curley IR, Wheeler MH, Thompson NW, Grant CS. The challenge of the middle mediastinal parathyroid. World J Surg 1988; 12: 818-824

2 Gaz RD, Doubler PB, Wang CA. The management of 50 unusual hyperfunctioning parathyroid glands. Surgery 1987; 102: 949-957

Standard surgical treatment of primary hyperparathyroidism until the 1990s:

Conventional Neck Exploration

2

Introduction

Sandström [1] first described a small gland located in the vicinity of the thyroid gland in 1880 and gave it the name of 'glandula parathyroidea'. The first anatomic description in humans was published by Welsh [2] in 1898, and by Halsted and Evans [3] in 1907. After the first successful parathyroid operation was performed by Doctor Felix Mendl in Vienna in 1925 for a patient with primary hyperparathyroidism (pHPT) and osteitis fibrosa cystica, parathyroidectomy has been the treatment of choice for patients with pHPT [4]. It was not until the late 1960s that most cases of pHPT were detected by routine biochemical screening rather than because of specific associated symptoms or complications such as renal colic, parathyroid bone disease, peptic ulcer disease, gout, or pancreatitis. Routine multichannel biochemical screening of serum calcium came to widespread use at the beginning of the 1970s, resulting in a rapidly increasing total number of patients diagnosed with mild to moderate hypercalcemia. Primary hyperparathyroidism is nowadays the most common cause of hypercalcemia in nonhospitalized patients and, along with (dissiminated) cancer, accounts for 90% of all patients with hypercalcemia [5].

Clinical Presentation and Diagnosis

Most patients are detected by routine screening before presenting with (severe) clinical symptoms. The diagnosis pHPT is based upon documentation of persistent hypercalcemia and elevated parathyroid hormone (PTH) level without hypocalciuria. Immunoassays for intact PTH using double-antibody methods are highly sensitive and represent a major advance in the diagnostic process [6]. The majority of patients with pHPT have unequivocal elevated PTH levels, whereas patients with hypercalcemia from other causes, such as malignancy and sarcoidosis have low, normal, or suppressed values [6]. Other tests that sometimes are useful (but not diagnostic) are the blood alkaline phosphatase level, which is elevated in high turnover parathyroid bone disease and the blood phosphate level which is decreased in about 50% of patients with pHPT. This, simultaneously with an increased blood chloride level (in about 40% of patients) elevates the chloride/phosphate ratio in most patients [7].

The clinical manifestation of pHPT varies from asymptomatic disease to a picture which has been described as 'painful bones, kidney stones, abdominal groans, psychic moans, and fatigue overtones'. Most patients (about 80%) are diagnosed

Table 1

Symptoms in patients with primary hyperparathyroidism.
Bone Pain
Constipation
Depression
Exhaustion
Fatigue
Joint pain
Loss of appetite
Memory loss
Nausea
Nocturia
Poliuria
Polydipsia
Renal colic
Weakness

with pHPT without having any symptoms or with subtle symptoms as fatigue and muscular weakness. **Table 1** shows the spectrum of symptoms which may be present in pHPT.

Anatomy and Embryology

The superior parathyroid glands originate along with the lateral lobes of the thyroid (ultimobranchial body) from the dorsal tips of the pharyngeal fourth pouch. Because the superior glands migrate only slightly their position is relatively constant, cephalad to the inferior thyroid artery and dorsal in respect to the recurrent laryngeal nerve. The inferior glands arise along with the thymus from the dorsal part of the third branchial pouch and migrate downward during fetal life. The position of the normal inferior parathyroid gland is less constant because it travels so far in embryonic life. It can be found anywhere from the angle of the jaw to the pericardium, but is found caudal to the inferior thyroid artery and ventral to the recurrent laryngeal nerve in approximately 55% of cases [8]. In addition, enlarged parathyroid glands may migrate secondarily in adult life and become ectopic. The superior gland tends to fall back and displace in a posterior and caudal direction. It descends along the tracheo-esophageal groove even

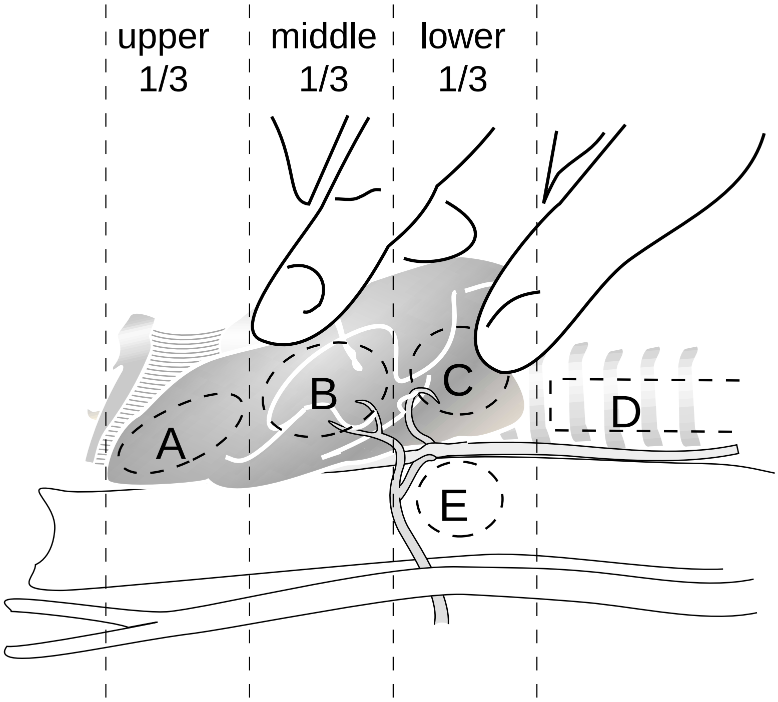


Figure 1 *The relative frequency with which the parathyroid glands are found in the various locations. The superior gland is usually (75%) found on the posterior portion of the middle third (B) of the thyroid. In about 9% the gland is found more cephalad at the upper pole (A) of the thyroid. The location of the inferior gland is more variable; approximately 55% is found on the posterior surface of the lower pole (C), 25% below the lower pole (thymus or lower) (D), 10% deep medio-posterior of the thyroid (E).*

as deep as the posterior mediastinum. The inferior parathyroid gland tends to move in an anterior-caudal direction and may descend in the anterior mediastinum [9].

The average weight of a normal parathyroid gland is 35-50 mg. Parathyroid glands are small (2-5 mm), usually yellowish-brown and sometimes look like fat, which make them difficult to find for the inexperienced operator. In approximately 75% of cases the superior gland is to be found on the posterior portion of the middle third of the thyroid. As already indicated the position of the normal inferior gland is more variable and can be found in approximately 75% of cases on the lateral or posterior surface of the lower pole of the thyroid gland, or not more than 0.5 cm below the lower pole [10] (**Figure 1**).

Parathyroidectomy

Surgery offers the only definitive treatment for patients with pHPT [11]. The primary goal of parathyroidectomy is to establish normocalcemia with minimal complications (these include persistent or recurrent hyperparathyroidism, postoperative transient or persistent hypoparathyroidism, and recurrent laryngeal nerve injury).
The gold standard in parathyroid surgery is the conventional neck exploration (CNE), a very safe procedure with success rates exceeding 95% and minimal morbidity (**Table 2**) [12 13 14 15 16]. The most important variable that influences the success of parathyroidectomy is the experience of the surgeon. The rate of persistent hyperparathyroidism can be as high as 30% in less experienced hands [17].

Conventional neck exploration is preferentially performed under general anesthesia with endotracheal intubation. The patient is positioned in supine position, the neck extended dorsally to provide maximal access to the neck. A low, symmetric Kocher transverse incision is made 3 to 4 cm cranial to the suprasternal notch. After incision of the platysma muscle, the strap muscles (m. sternohyoid, m. sternothyroid) are divided in the median raphae, separated from each other and may be cleaved. The sternocleidomastoid muscle and internal jugular vein are lateralized. The fascia between common carotid sheath and thyroid is opened alongside the carotid artery in order to mobilize the thyroid gland in medioventral direction, whereafter the loose areolar tissue of the tracheoesophageal groove is entered. Care is taken in identifying the delicate recurrent laryngeal nerve.
After identification of the four parathyroids, the adenoma(s) is resected and sent for histological examination. The assessment whether a parathyroid is normal or diseased is determined by the surgeon and is based upon macroscopical features such as size and color. Some authors rely on microscopical features in frozen section to distinguish adenomas from hyperplastic glands [18 19]. However, no single criterium has irrefutably proven to be useful in discriminating between adenoma and hyperplasia [20]. Therefore, we agree with the statement that the role of the pathologist intraoperatively is limited simply to the identification of parathyroid tissue [21].

Difficulties associated with parathyroid surgery relate to the variety in location, and to a lesser extent, the number of the (diseased) glands, and to the problem of differentiating normal glands from slightly diseased ones. In an extensive postmortem study Gilmour [22] found that 80% of individuals had four parathyroids, 6% had five and 13% had three. Others report different frequencies of supernumerary glands: Boyd [23] found five or six glands in 14%, Alveryd [24] reported fewer than four glands in less than 1%. Without neglecting these figures, it is of utmost importance to identify four parathyroids. Even if an adenoma and two normal parathyroids are identified the surgeon should endeavor to find the unidentified parathyroid,

Table 2 Success rate after Conventional Neck Exploration, review of literature.

Author	n	period	median follow up	success (%)	morbidity (%)	mortality (%)
Bruining HA, et al. [13]	615	1950-1979	5.6 years	96.4	laryngeal nerve 0 hypocalcemia 1.1	0
Saaka MB, et al. [15]	316	1960-1986	6 years	92.1	laryngeal nerve 1 hypocalcemia 0.8	0
Low RA, Katz AD [16]	866	1960-1997	1-96 months	98.2	laryngeal nerve 0.3 hypocalcemia 1	0.3
Russel CF, Edis AJ [12]	500	1974 -1980	NA	92.2	laryngeal nerve 0.2 hypocalcemia 0	0.2
Heerden JA, Grant CS [14]	384	1983-1984	4 years	99.6	laryngeal nerve 0.8 hypocalcemia 0.3	0.3

laryngeal nerve: damage to the recurrent laryngeal nerve.

NA: not available.

because missing at its normal localization can indicate a migrated second enlarged parathyroid. If during exploration one or more parathyroids are missing or the adenoma cannot be found the following rules should be remembered. Firstly, as has been succinctly stated by Rothmund [25], the majority of all parathyroids are located within a 1-2 cm circle around the intersection of the inferior thyroid artery and the recurrent laryngeal nerve. The superior gland situated cephalad to the artery and dorsal in respect to the nerve, the inferior caudal to the artery and ventral to the nerve [26]. Secondly: it may be assumed that the gland on the contralateral side is located symmetrically to the one found at the 'identified side'. Thirdly: If the missing adenoma is of superior origin, the space dorsal to the thyroid gland and the oesophagotracheal groove should be explored. The common origin of the superior parathyroid and thyroid accounts for the occasional intrathyroidal location found in less than 1% of all cases [25 26]. The tongue of the thymus (thyrothymic ligament) should be explored for a missing inferior gland since this is the second most common location after the lower pole of the thyroid. If the adenoma is still missing after thymectomy an intrathyroidal parathyroid should be considered necessitating thyroidotomy or lobal thyroidectomy. However rare, a missing inferior adenoma can be found anywhere along the path of descensus, from the angle of the jaw to the pericardium [10 25]. Finally, a primary sternotomy should only be considered after a thourough, systematic, but negative exploration in patients with life threatening hypercalcemia [27].

A major and recurrent problem during exploration is the differentiation between an adenoma and a hyperplastic gland, or single gland disease from multiple gland disease. Since microscopic examination durante operationem is of no added value, making decision relies upon the macroscopic features and thus on the surgeon's judgement and experience. Classically, an adenoma has been defined as an enlarged gland with a rim of normal tissue. However, this histological appearance can be found in cases of hyperplasia as well. Significant differences in histological appearance could not be demonstrated in 236 patients with pHPT by Bonjer et al [20].

Preoperative Imaging Studies

Numerous localization techniques have been used to identify the site of the abnormal parathyroid gland preoperatively, including ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), thallium201-technetium-Tc99m pertechnetate scanning (ThTc) and sestamibi-technetium99m scintigraphy (Sestamibi), and selective venous catherization for measurements of PTH levels.
High-resolution ultrasonography is easy to perform and is well tolerated by the patient. It does not require injection of contrast, does not emit radiation, can be done quickly and is inexpensive. Unfortunately, the retrosternal, retroesophageal, retrotracheal and deep cervical glands are difficult to locate by US. The sensitivity varies according to the ultrasonographer's experience, the frequency of the transducer, the resolution of the image, and the size of the parathyroid gland [28].
Computed tomography is relatively expensive, exposes the patient to radiation, and requires administration of (a) contrast agent(s) to obtain the highest resolution. The sensitivity of CT reportedly ranges from 41 to 86%, as compared to 57-90% [29 32] for MRI. Other advantages of MRI over CT are that the use of contrast is avoided and shoulder artefacts are not a problem.
Thallium201-technetium-Tc99m pertechnetate scanning is reported to be moderately accurate with sensitivity rates ranging 25 to 70% [29 33], whereas Sestamibi is superior with reported sensitivity rates reaching 100% in solitary disease [34 35].
Radionuclide scintigraphy is associated with low risk and minimum irradiation, and is minimally operator dependent. However, due to the high cost, its use should be restricted to a selected group of patients.
Selective PTH sampling is an invasive, expensive localization method requiring an expert radiologist. This method should, therefore, be limited to the reoperative case.

Progressive development of imaging modalities over the last ten years have made the various techniques increasingly reliable. The pace technical development should raise the accuracy and sensitivity rates of localization studies and anticipates future image-guided surgical procedures.

Discussion

Since pHPT can be diagnosed with nearly 100% accuracy and successfully treated in more than 95% of patients, surgery is the choice of treatment. Until now the gold standard in parathyroid surgery has been CNE. Routine localization studies are of no added value, since sensitivity rates in localizatory studies (reaching 85% maximum) are inferior to success rates in CNE [38]. Furthermore, accuracy of imaging techniques decreases in multiglandular disease and is therefore of little use in predicting whether a patient has uniglandular or multiglandular disease [29 31 39]. Preoperative localization may even mislead the less experienced surgeon, who might fail to identify all involved parathyroid glands [35].

With success rates exceeding 95% and virtually no complications nothing more seems to be desired. Nevertheless, since the early 1980s authors have been increasingly propagating less invasive techniques [36 37] (unilateral exploration), in order to reduce operation time and admission days, decrease operative risk during reexploration and to obtain better cosmetic results. They rely upon the high incidence of solitary adenoma (approximately 85%) and improved resolution in preoperative imaging modalities. 'Bilateralists' however, oppose such an approach because of the incidence of multiple gland disease which may be, in their opinion, as high as 30% [13]. Furthermore they are critical as far as the accuracy of localization procedures is concerned.

The ability to document PTH concentration during operation, first described by Nusbaum [40], was further developed in the early 1990s. The use of an intraoperative PTH assay could prove beneficial in the surgical management of pHPT. The biochemical confirmation of complete removal of all hyperfunctioning tissue allows less than bilateral neck explorations. Despite their helpfulness, these intraoperative assays have not gained widespread acceptance. The short half-life of isotopes and thus limiting shelf-life of these intraoperative PTH assays; the necessary safety precautions (including proper disposal of waste products); a false negative rate of 15%; and high costs initially limited its use to a few specialized centers [37].

The diagnosis pHPT is based upon biochemically proven hypercalcemia with inappropiate high levels of PTH. The treatment of choice is CNE, a highly effective procedure associated with minimal morbidity. However, because pHPT is caused by a solitary adenoma in at least 85%, and presently available localization procedures are increasingly accurate, unnecessary extensive dissection is undertaken in the vast majority of patients. The ability to ascertain success of parathyroidectomy by presently available reliable and affordable intraoperative PTH assays will lead undoubtedly towards more limited forms of parathyroidectomy.

References

1 Sandrström I. Om en ny körtel hos människan och åtskilliga däggdjur. Uppsala Läk-Fören Förh 1879-80; 15: 441-471

2 Welsh DA. Concerning the parathyroid glands: a critical anatomical and experimental study. J Anat Physiol 1898; 32: 292-307

3 Halsted WS, Evans HM. The parathyroid glandulas: their body supply, and their preservation in operation upon the thyroid gland. Ann Surg 1907; 46: 489-501

4 Goldman L, Gordon GS, Roof BS. The parathyroids. Cur Prob Surg. St Louis, Mosby; 1971: 1-64

5 Clark OH. Management of primary hyperparathyroidism. Adv Endocrinol Metab 1995; 6: 1-16

6 Budayr AA, Nissenson RA, Klei RF, et al. Increased serum levels of a parathyroid hormone-like protein in malignancy-associated hypercalcemia. Ann Intern Med 1989; 10: 807-812

7 Reeves CD, Palmer F, Bacchus H, Longerbeam JK. Differential diagnosis of hypercalcemia by chloride/phosphate ratio. Am J Surg 1975; 130: 166-171

8 Gilmour JR. The embryology of the parathyroid glands, the thymus and certain associated rudiments. J Pathol 1937; 45: 507-521

9 Curley IR, Wheeler MH, Thompson NW, Grant CS. The challenge of the middle mediastinal parathyroid. World J Surg 1988; 12: 818-824

10 Kaplan EL, Yashiro T, Salti G. Primary hyperparathyroidism in the 1990s; Choice of surgical procedures for this disease. Ann Surg 1992; 215: 300-317

11 Diagnosis and management of asymptomatic primary hyperparathyroidism. National Institute of Health Consensus development conference statement. J Bone Miner Res 1991; 6: 59-63

12 Russel CF, Edis AJ. Surgery for primary hyperparathyroidism: experience with 500 consecutive cases and evaluation of the role of surgery in the asymptomatic patient. Br J Surg 1982; 69: 244-247

13 Bruining HA, van Houten H, Juttmann JR, et al. Results of operative treatment of 615 patients with primary hyperparathyroidism. World J Surg 1981; 5: 85-90

14 van Heerden JA, Grant CS. Surgical treatment of primary hyperparathyroidism: an institutional perspective. World J Surg 1981; 15: 688-692

15 Saaka MB, Sellke FW, Kelly TR. Primary hyperparathyroidism. Surg Gynaecol Obstet 1988; 166: 333-337

16 Low RA, Katz AD. Parathyroidectomy via bilateral cervical exploration: a retrospective review of 866 cases. Head and Neck 1998; 20: 583-587

17 Malmaeus J, Granberg PO, Halvorsen J, et al. Parathyroid surgery in Scandinavia. Acta Chir Scand 1988; 154: 409-413

18 Rudberg C, Akerström G, Palmer M, et al. Late results of operation for primary hyperparathyroidism in 441 patients. Surgery 1986; 99: 643-651

19 Cooke TJC, Boey JH, Sweeney EC, et al. Parathyroidectomy: extent of resection and late results. Br J Surg 1977; 64: 153-157

20 Bonjer HJ, Bruining HA, Birgenhager JC, et al. Single and multigland disease in primary hyperparathyroidism: Clinical follow-up, histopathology, and flow symmetric DNA analysis. World J Surg 1992; 16: 737-743

21 Nishiyama RH. The intraoperative diagnosis of parathyroid lesions. Acta Chir Aust 1994; 112: 8-14

22 Gilmour JR. The gross anatomy of the parathyroid glands. J Pathol Bacteriol 1938; 46: 133-149

23 Boyd JD. Development of the thyroid and parathyroid glands and the thymus. Ann R Coll Surg Eng 1950; 7: 455-461

24 Alveryd A. Parathyroid glands in thyroid surgery. I Anatomy of parathyroid glands II Postoperative hypoparathyroidism, identification and autotransplantation of parathyroid glands. Acta Chir Scand 1968; 389: 1-120

25 Rothmund M. A parathyroid adenoma cannot be found during neck exploration of a patient with presumed primary hyperparathroidism. Br J Surg 1999; 86: 725-726

26 Akerström G, Malmaeus J, Bergström R. Surgical anatomy of human parathyroid glands. Surgery 1984; 95: 14-21

27 Bonjer HJ, Bruining HA. Technique of parathyroidectomy. Clark OH, Duh QY. Textbook of Endocrine Surgery. Philadelphia: WB Saunders Company; 1997: 347-356

28 Gooding GAW. Sonography of the thyroid and parathyroid. Radiol Clin North Am 1993; 31: 967-989

29 Miller DL. Preoperative localization and interventional treatment of parathyroid tumors: when and how? World J Surg 1991; 15: 706-715

30 Roses DF, Sudarsky LA, Sanger J, et al. The use of operative localization of adenomas of the parathyroid gland by thallium-technetium, high-resolution ultrasonography and computed tomography. Surg Gynecol Obstet 1989; 168: 99-106

31 Krubsack AJ, Wilson SD, Lawson TC, et al. Prospective comparison of radionuclide, computed tomography and sonographic localization of parathyroid tumors. World J Surg 1986; 10: 579-585

32 Erdman WA, Breslau NA, Weinreb JC, et al. Noninvasive localization of parathyroid adenomas: a comparison of X-ray computerized tomography, ultrasound, scintigraphy and MRI. Magn Reson Imag 1989; 7: 189-194

33 Price DC. Radioisotopic evaluation of the thyroid and parathyroids. Radiol Clin North Am 1993; 31: 991-1015

34 Thulé P, Tharoke K, Vasant J, et al. Preoperative localization of parathyroid tissue with technetium-99m sestamibi 123I substraction scanning. J Clin Endocrinol Metab 1994; 78: 77-82

35 Casas AT, Burke GJ, Mansberger AR jr, Wei JP. Impact of technetium-99m sestamibi localization on operative time and success of operations for primary hyperparathyroidism. Am Surg 1994; 60: 12-16

36 Tibblin S, Bondeeson AG, Ljungberg O. Unilateral parathyroidectomy in hyperparathyroidism due to single adenoma. Ann Surg 1982; 195: 245-252

37 Irvin GL, Prudhomme DL, Deriso GT, et al. A new approach to parathyroidectomy. Ann Surg 1994; 219: 574-581

38 Roe SM, Burns P, Graham LD, et al. Cost-effectiveness of preoperative localization studies in primary hyperparathyroid disease. Ann Surg 1994; 219: 582-586

39 Roth SI. Pathology of the parathyroids in hyperparathyroidism: discussion of recent advances in the anatomy and pathology of the parathyroid glands. Arch Pathol 1962; 73: 495-504

40 Nusbaum SR, Thompson AR, Hutcheson KA, et al. Intraoperative measurement of parathyroid hormone in the surgical management of hyperparathyroidism. Surgery 1988; 104: 1121-1127

03. hoofdstuk 03 23-07-2001 10:04 Pagina 19

Hypothesis and Objectives

3

Based on the knowledge that in the vast majority (>85%) of patients primary hyperparathyroidism is caused by a single parathyroid adenoma, and stimulated by the potential for preoperative localization of present imaging technology (illustrated in chapter one) the following hypothesis was formulated:

A substantial group of patients with primary hyperparathyroidism can be successfully treated by limited access surgery after preoperative localization studies and may thus be spared unnecessary extensive dissection (conventional neck exploration).

To confirm this hypothesis the following questions were addressed in the studies presented in this thesis:

1 a) Is minimally invasive adenomectomy a safe and reliable alternative to conventional neck exploration ?
b) Is minimally invasive adenomectomy associated with higher morbidity compared to conventional neck exploration ?
c) In how many patients can conventional neck exploration be replaced by minimally invasive adenomectomy ?
(chapter 4: Direct, minimally invasive adenomectomy for primary hyperparathyroidism: an alternative to conventional neck exploration ?)

2 Provided minimally invasive adenomectomy is validated as a safe alternative to conventional neck exploration, would that imply that this technique should be restricted to symptomatic patients, or should asymptomatic patients also be considered for this procedure as well ?
(chapter 5: Strategy in asymptomatic and mildly symptomatic primary hyperparathyroidism, new arguments for the surgical option)

3 How reliable is Doppler ultrasonography combined with computed tomography, and Doppler ultrasonography with selective supplemental computed tomography in the selection for minimally invasive adenomectomy ?
(chapter 6: Minimally invasive surgery of solitary parathyroid adenomas in patients with primary hyperparathyroidism; Role of ultrasonography with supplemental computed tomography)

4 a) Will a modification of standardized parathormone assay result in a quick and reliable assay to ascertain success of parathyroid surgery ?
b) And can it be used on a routinely base in the surgical treatment of primary hyperparathyroidism ?
(chapter 7: Peroperative PTH testing: confirmation of successful surgical treatment of primary hyperparathyroidism)

5 a) How reliable are commercially available non-portable parathormone assays in predicting surgical outcome ?
b) Can these tests serve as an alternative for (expensive) commercially available portable assays ?
(chapter 8: Perioperative parathormone assessment during surgery for primary hyperparathyroidism; Comparison of four techniques)

6 a) What are the costs of minimally invasive adenomectomy and conventional neck exploration, taken from a hospital point of view ?
b) Which appreciable variables can be identified and what is the degree of change required to eliminate differences in costs ?
(chapter 9: Cost-analysis of minimally invasive surgery and conventional neck exploration for primary hyperparathyroidism)

Direct, minimally invasive adenomectomy for primary hyperparathyroidism:

An alternative to conventional neck exploration ?

4

Smit PC, Borel Rinkes IHM, van Dalen A, van Vroonhoven TJMV. Direct, minimally invasive adenomectomy for primary hyperparathyroidism: an alternative to conventional neck exploration ? Annals of Surgery 2000 ; 231 : 559 - 565

Abstract

Objective To evaluate the feasibility and efficacy of a direct, minimally invasive adenomectomy (MIA) as an alternative to conventional neck exploration (CNE) in patients with primary hyperparathyroidism.

Summary Background Data Because primary hyperparathyroidism is caused by a solitary adenoma in 85 to 90% of patients, a direct adenomectomy through a mini-incision would theoretically suffice whenever an adenoma is correctly localized on preoperative imaging. If effective, a less invasive method could spare the patient an unnecessary bilateral neck exploration, thus saving time and rendering future surgical procedures in the neck less problematic.

Methods Between October 1994 and October 1998, 110 consecutive patients with biochemically proven primary hyperparathyroidism who were to undergo surgery were enrolled in this study. Ultrasound and spiral CT were routinely performed as standard preoperative imaging modalities in the first series of 65 patients. In the second series of 45 patients, ultrasound was performed as a sole initial modality; it was supplemented by CT only in case of inconclusive test results. If test results were unequivocal (one adenoma) the patient was offered MIA. CNE was performed if the results were equivocal or if multiglandular disease was suspected.

Results Overall, 84 patients were selected for MIA and 26 for CNE. In the first series, 2 MIA procedures (2/51) were converted to CNE because of negative perioperative findings. All 65 procedures resulted in normocalcemia. In the second series, all but 5 (4/33 MIAs, 1/12 CNEs) resulted in normocalcemia. A reexploration (CNE) was performed in three patients, resulting in normocalcemia after resection of a second or third adenoma. Two patients are still awaiting reexploration. In both series together, 78 of the 110 patients were successfully treated with MIA and spared a CNE.

Conclusion MIA is a safe and effective alternative to CNE that may replace CNE in approximately two thirds of all patients.

Introduction

Conventional treatment for primary hyperparathyroidism (pHPT) consists of systematic bilateral neck exploration, identification of all parathyroid glands, and removal of all pathologically enlarged, hyperfunctioning parathyroid tissue [1]. Because this conventional neck exploration (CNE) is associated with a minimal death rate, a low complication rate, and cure rates of 90 to 97%, it is generally considered an effective and safe procedure leaving little room for improvement [1 2].

However, various authors have confirmed that pHPT is caused by a solitary adenoma in 85 to 90% of cases [1 2 3 4]. In these patients, removal of the affected parathyroid gland alone through a mini-incision, would theoretically suffice. Thus, unnecessary exploration of normal parathyroids, making subsequent surgery in the thyroid region unattractive and more prone to complications, might be avoided. Few reports have been published on strategies of less invasive surgery for pHPT, most of which have included unilateral exploration [5 6]. Only the study of Chapuis et al. [3] describes a truly minimally invasive strategy, with mini-incision over the adenoma. Using this procedure, the authors reported they could avoid CNE in approximately 40% of their patients.

Clearly, for such a direct, minimally invasive adenomectomy (MIA) to be successful, optimal preoperative imaging is a prerequisite. This imaging should not only accurately localize pathologically enlarged parathyroid glands, but should also be capable of aiding in the selection of patients for the direct approach by differentiating between solitary and multiglandular disease. Although many imaging techniques have been reported for visualization of hyperfunctioning parathyroids, with varying degrees of success, none has proved sufficiently accurate to revolutionize surgical management in patients with pHPT, with the exception of reoperations [7 8]. Nevertheless, recent work from our group has indicated that preoperative imaging by combined ultrasonography and CT scanning, including the use of cinevision technology, appears to be able to improve sensitivity and specificity rates to acceptable levels [4]. The present study represents a prospective evaluation of MIA in over 100 patients with pHPT. Initially, combined imaging was used routinely. In the second group of patients, we tried to determine whether ultrasound could be used as the sole initial imaging modality, basing the need for subsequent CT scanning on the ultrasound findings.

Methods

Patients

Consecutive patients with biochemically proven pHPT who were to undergo surgery were enrolled in this prospective study. Informed consent was obtained. Patients with previous (para)thyroid surgery were excluded. Between October 1994 and October 1998, 110 patients with pHPT were included. The investigated group involved 27 male patients and 83 female patients with a median age of 59.5 years (range 17-84). The median serum calcium level was 2.85 mmol/L (2.35-3.80; normal 2.20-2.60) and the median serum parathyroid hormone (PTH) was 12.8 pmol/L (4.9-234; normal <8 in normocalcemic state). All patients underwent preoperative parathyroid imaging.

In the first series of 65 patients (group A), both ultrasonography and CT scanning of the neck were routinely performed as standard preoperative imaging modalities. In the second series of 45 patients (group B), ultrasound was done as the sole initial imaging modality. When the ultrasound results were inconclusive, additional CT scanning was performed. The imaging data of each individual patient were thoroughly discussed by the radiologist and the surgeon. If there was unequivocal radiologic identification of a solitary adenoma, the patient was offered an adenomectomy with MIA. In contrast, when the test results were equivocal, or if multiglandular disease was suspected, the patient underwent a systematic bilateral neck exploration. This protocol has been described elsewhere [9]. An exploration was defined as being successful when a normocalcemic state (or hypocalcemia) was documented on the first postoperative day and confirmed after a minimal follow-up of 1 month. The preoperative findings on imaging were compared with intraoperative observations and postoperative test results (eg serum calcium, histology).

Ultrasound examinations were performed using a high-end real time unit (ATL, HDI 900 and 3000, Transducers L5-10 and L7-4; Advanced Technical Laboratories, Bothell, Washington, USA) with color Doppler mode. All examinations were performed by the same experienced radiologist (AvD). The patient was positioned in the same way as for surgery: in supine position with the neck in hyperextension. Modern ultrasound systems with their discriminatory capacity of structures measuring 3 mm or more, still cannot visualize normal parathyroid glands. However, enlarged, hyperfunctional parathyroids can be discerned not only on the basis of their size and oval shape, but also because of their characteristic ultrasound features, including hypoechogenicity, typical intraglandular blood flow, movability, and non-compressibility [4]. All ultrasound findings regarding the location, size and shape of each parathyroid (adenoma), concomitant thyroid disease,

and other abnormalities were recorded and stored in a database.
Spiral CT scanning (Tomoscan 7000; Philips Medical Systems, Eindhoven, The Netherlands) was performed after intravenous administration of a contrast bolus (90 mL Isovist 300 (Schering M, Berlin, Germany); rate 2 mL/sec, delay 25 sec) using a slice thickness of 5 mm and a reconstruction index of 3 mm. Again, parathyroid adenomas were recognized partly by their anatomical position and partly by their vascularity. Essential additional information was obtained from image analysis at the computer workstation (Easy Vision, Philips Medical Systems, Best, The Netherlands). This allows reconstruction of a scanned volume in the cine loop motion. With this dynamic reconstruction, it is possible to go up and down through the scanned volume, making it easier to identify anatomical details that would otherwise be difficult to discern.

All explorations were carried out under general anesthesia by the same surgical team. The duration (incision to closure) of each exploration was monitored, together with the exact position of the excised structure.
Minimally invasive adenomectomy was performed through a 2-cm-long transverse incision at the medial border of the sternocleidomastoid muscle, precisely over the site where the enlarged gland had been located by preoperative ultrasound. With the sternocleidomastoid muscle and internal jugular vein retracted laterally, and the strap muscles medially, the thyroid gland was grasped in Ellis forceps and held in medioventral direction. This allowed the surgeon to reach the loose areolar tissue of the tracheoesophageal groove (**Figure 1**). After identification of the enlarged gland, it was excised in toto and its vascular pedicle ligated. No wound drains were used. Conventional neck exploration was carried out through a transverse collar incision. A bilateral, systematic exploration was done identifying as many parathyroid glands as possible before removal of the enlarged, hyperfunctioning gland or glands. Surgical findings, including the size, weight, and location of each gland excised, were noted before preparation for histological examination.

Immediately after surgery, blood samples were taken at regular intervals. Procedure-related complications were documented and followed in time. Patients were discharged as soon as their clinical condition permitted; one criterion for discharge was a serum calcium level of 2.20 mmol/L or more, which was generally achieved on the first or second postoperative day. All patients were seen on follow up visits after 1 week and 1 month; after that, follow-up was continued by the patient's physician. At one month after surgery, the surgical procedure was determined to be successful or unsuccessful, as defined above. If hypercalcemia persisted, the patient was scheduled to undergo a reexploration.
Recently, we have developed a rapid PTH test for intraoperative assessment [10].

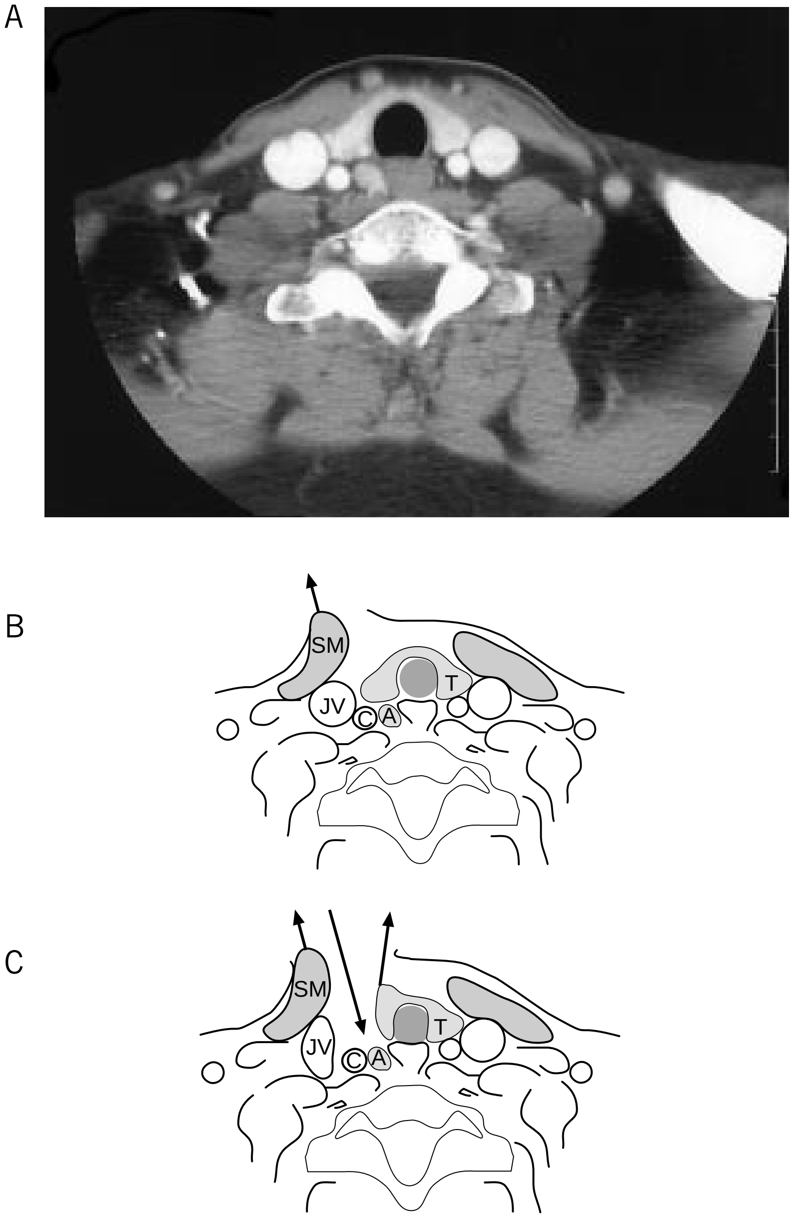


Figure 1 *Cross section images of spiral CT scanning (A) and corresponding schematic drawings (B, C) to depict the route used for the direct approach of a parathyroid adenoma. (B) Lateral retraction of sternocleidomastoid muscle (SM). (C) Lateral retraction of SM plus internal jugular vein (JV), and medioventral retraction of the right lobe of the thyroid gland (T), allows direct approach (downward arrow) of a parathyroid adenoma (A). C, common carotid artery.*

This is useful, because the half-life of this hormone is approximately 5 minutes. The test involves a modification of the computerized immunometric method using chemoluminescence for detection. Although this test was not a subject of the present study, with the use of this test surgery was found to have failed in some of the patients later in this series, and could, therefore, undergo immediate conventional reexploration.

Although all resected parathyroid glands were examined histologically, histological classification as 'adenoma' or 'hyperplasia' has been found to correlate poorly with 'single' versus 'multiglandular' disease [11]. In fact, earlier work has shown that the distinction between the two entities may be suppositional [12 13]. Based on these observations, we defined each enlarged, hyperfunctioning parathyroid gland as adenoma for the purpose of this study.

Results

Overall, 84 patients underwent MIA and 26 CNE. **Table 1** lists the main characteristics of each procedure. Two patients who underwent MIA had transient neuropraxia of the ipsilateral recurrent laryngeal nerve lasting approximately 2 and 5 months. Both patients had large adenomas in the lower region of the neck. Oral supplementation for transient hypocalcemia was required in five 5 patients (two after CNE, three after MIA). On follow-up at 1 week and 1 month after surgery, serum calcium levels were similar to those on day 1. So far, no late recurrences have been identified after a median follow-up of 23.5 months (range 4-48).

The excised adenomas varied from 90 to 16,020 mg (median 560; normal <40 mg). All resected adenomas were confirmed histologically. **Table 2** shows the number of adenomas retrieved in each treatment group. Ninety percent of the patients in this series had solitary adenomas; 10% had multiple adenomas.

In group A, all 65 patients underwent ultrasound investigation according to protocol. Four patients did not have spiral CT scanning because of pregnancy or claustrophobia. Based on unequivocal localization and identification of a solitary adenoma on imaging, 51 patients were selected for MIA. The remaining 14 patients underwent CNE. Because of negative perioperative findings, two MIA procedures were converted into CNE. In one instance, the causative adenoma was found in a different location than predicted on imaging, as a result of significant multinodular enlargement of the thyroid. The adenoma in the second patient was localized correctly, but missed during MIA. All 65 procedures resulted in normocalcemia at 1 day, 1 week and 1 month after surgery (**Table 3**). Nine patients who

Table 1 Treatment characteristics.

	MIA	CNE	
Patients (n)	84	26	
Operating time	20 [8-35]	80 [20-120]	p<0.05
Hospital stay	1.7 [1-5]	3.0 [1-8]	p<0.05
Complications			
Transient RLN*-neuropraxia	2	-	
Transient hypocalcemia	2	3	
Serum calcium level (mmol/L)			
Before surgery	2.85 [2.35-3.55]	2.82 [2.50-3.80]	
1 day after surgery	2.25 [1.61-2.80]	2.29 [1.83-2.61]	

Data are presented as median values [range].

*RLN= recurrent laryngeal nerve.

Table 2 Number of enlarged parathyroid glands (adenomas) retrieved.

	Number of enlarged glands		
Procedure	**1**	≥ **2**	**total**
MIA*	81	3	84
CNE†	18	8	26
Total	99	11	110

*MIA= minimally invasive adenomectomy, †CNE= conventional neck exploration.

Numbers represent numbers of patients.

were selected for CNE actually had solitary adenomas. Thus, combined imaging with ultrasound and CT (including cinevision) had a sensitivity of 84%, a specificity of 72%, and a positive predictive value of 96% (**Table 4**).

In group B (n=45), a supplementary spiral CT was performed in 27 patients because of inconclusive test results on ultrasonography. In the other 18 patients a solitary adenoma was diagnosed on ultrasound, and MIA was advised. After CT

Table 3 Results of surgical procedure after selection by preoperative US and CT (group A).

	Primary procedure				Secondary procedure	
	n	**succ.**	**(%)**	**fail.**	**succ.**	**fail.**
MIA*	51	49	(96)	2	2‡	-
CNE†	14	14	(100)	-	-	-

*MIA= minimally invasive adenomectomy, †CNE= conventional neck exploration.

‡Both secondary procedures were done immediately.

Succ.= successful, fail.= failure.

Table 4 Perioperative outcome of preoperative imaging by combined ultrasound and CT (group A).

	MIA possible **		
Preoperative advice	yes	no	total
MIA*	49	2	51
CNE†	9	5	14
Total	58	7	65

*MIA= minimally invasive adenomectomy, †CNE= conventional neck exploration.

**Defined as a solitary adenoma at the predicted site surgically resectable through a minimal incision.

scanning, another 15 patients were selected to undergo MIA; the remaining 12 underwent CNE (**Table 5**). In this group, MIA was unsuccessful in four patients, three of whom had undergone ultrasonography as the sole preoperative imaging modality. Two of those in whom surgery failed were identified during surgery by rapid PTH testing. These two underwent immediate conventional exploration. In one patient, a second adenoma was ultimately found inside a thyroid cyst; in the other patient a smaller-than-anticipated adenoma had been removed during MIA, whereas the second, larger adenoma that had been seen on imaging was located more dorsally in the direct vicinity of the first lesion. Both explorations resulted in persistent normocalcemia as well as normal serum PTH levels. The other two cases in which surgery failed involved patients in whom single adenomas fitting

Table 5 Results of surgical procedure after selection by preoperative ultrasound and selective CT.

	Primary procedure				Secondary procedure		
	n	**succ.**	**(%)**	**fail.**	**succ.**	**fail.**	**await.**
MIA*	33	29	(88)	4	3	-	1
CNE†	12	11	(91)	1	1	-	-

*MIA= minimally invasive adenomectomy, †CNE= conventional neck exploration.

succ.= successful, fail.= failure, await.= awaiting secondary exploration.

Table 6 Perioperative outcome of preoperative imaging by ultrasound and selective CT.

	MIA possible **		
Preoperative advice	yes	no	total
MIA*	29	4	33
CNE†	9	3	12
Total	38	7	45

*MIA= minimally invasive adenomectomy, †CNE= conventional neck exploration.

** Defined as a solitary adenoma at the predicted site surgically resectable through a minimal incision.

the preoperative imaging results were removed during MIA, but hypercalcemia persisted on follow-up. One of these patients underwent successful reexploration, during which a second enlarged gland was retrieved. The other patient is awaiting further surgical exploration. Conventional neck exploration failed in one patient as a result of a missed third enlarged parathyroid gland in the thymus. As shown in **Table 6**, ultrasound as the sole initial preoperative imaging modality in this series resulted in a sensitivity of 76%, a specificity of 43%, and a positive predictive value of 88%.

The overall success rate of MIA was 93% (96% in group A, 88% in group B). The overall success rate for CNE was 96%.

Discussion

Our data confirm, once again, the high frequency (85-90%) of solitary adenomas in patients with pHPT [1 2 3 4]. Considering the number of successful MIA procedures as a function of the total number of patients who undergo surgical treatment for pHPT, CNE could be replaced by MIA in 71% of all patients (78/110): 75% of patients in group A (49/65) and 64% of patients in group B (29/45). Clearly, these figures justify the minimally invasive approach described here, which is characterized by a small incision in the skin directly over the affected parathyroid gland, as marked by preoperative ultrasound. The technique uses anatomical planes to reach the adenoma with virtually no unnecessary dissection. This is reflected by the short duration of the procedure. However, experience in this type of surgery is critical, because identification and retrieval of the enlarged gland through a mini-incision are delicate procedures.

The advantages of MIA are clear. The principle of minimal dissection when possible and conversion to CNE if necessary poses the least possible risk of complications, including minimal risk to the recurrent nerve and the other (normal) parathyroid glands. It also makes subsequent surgery in the (para)thyroid region far less complicated than after CNE. Minimally invasive adenomectomy takes significantly less time and is cosmetically attractive, and it could easily be performed in a same-day surgery setting (and eventually under local anesthesia) in selected patients.

Costs must be taken in consideration before any new approach can be definitely evaluated, and the costs, including direct and indirect costs, of MIA versus CNE are the subject of an ongoing study in our department. The additional costs of preoperative ultrasound and CT in every patient undergoing parathyroid surgery may be neutralized by the much shorter operative time and by the shorter hospital stay, with same-day surgery in selected patients. Intraoperative PTH measurment is not specific to this new approach; rather, it should be used in every parathyroid surgical procedure to prevent persisting hyperparathyroidism and the subsequent need for reoperation.

Although the failure rate of MIA is low (4% in this series) if the optimal imaging strategy is routinely followed, one could argue that the procedure might not be as effective as CNE in experienced hands. We believe, however, that MIA in similarly experienced hands does not impose any undue risk for the patient, since the worst outcome would still be a conventional exploration at a later stage, which is currently the standard operation for pHPT.

The use of rapid PTH testing will undoubtedly make both the patient and the surgeon even more comfortable with the concept of MIA, because it allows direct confirmation of success [14 15 16]. The surgeon can now be immediately aware of a failure, should it occur, and may convert immediately to CNE to attain normocalcemia and euparathyroidism. We have recently developed such a quick PTH-test and have included it as a standard perioperative measure [10]. Because this inexpensive test requires approximately 40 minutes, we use the following protocol. Eight minutes after adenomectomy, blood is taken for PTH-testing after which general anesthesia is ended and the patient is brought to the recovery room. Only when the PTH test has confirmed the MIA as successful is the patient allowed to leave the recovery room. If the PTH results are unsatisfactory, the patient can be returned to the next available operation room for subsequent CNE. This possibility is routinely discussed with the patient before surgery. The addition of routine perioperative PTH measurement should result in a nearly 100% immediate success rate.

Our data show that the success rate of MIA depends on the imaging performed before surgery. The sensitivity and specificity rates of combined US and CT (84 and 72%, respectively) are higher than those reported thus far for these modalities [7 8 17 18 19]. This may be explained in part by the fact that we adhered strictly to a combined imaging protocol in a prospective fashion, as opposed to the retrospective nature of most other investigations. The thorough discussion of each patient by all members of the multidisciplinary team and the preoperative ultrasound-guided marking of the skin over the suspected adenoma also contributed to this discrepancy.
In addition, the technological features of the ultrasound and CT devices played a significant role. The use of CT imaging in cinevision mode (i.e., repeatedly going up and down through the field of interest at the CT work station) is a major advance in parathyroid imaging and a magnificent aid in preoperative planning.

In this series, initial imaging with ultrasound alone, followed by CT only if dictated by the ultrasound findings, produced inferior accuracy compared with the combined imaging strategy. This finding was contrary to our expectation but was in concordance with other published data [3 8]. Specifically, three of the four failures occurred in patients who had undergone only ultrasound, suggesting that selection for CT by ultrasound is less reliable. Most importantly, the presence of multinodular thyroid enlargement is a major obstacle for ultrasonographic examination [4]. Based on our results presented, we do not support the concept of routine ultrasound alone, followed by CT only in selected patients. In fact, once the data from series B became available and turned out to be so much inferior to those of series A, we returned to the standard preoperative regimen of both CT and ultrasound.

Recent advances in radionuclide scintigraphy, including the use of 99mTechnetium-labeled sestamibi and other cationic complexes, have led to a promising increase in preoperative localization of parathyroid adenomas, with reported sensitivity rates of more than 85% [20 21]. Probe-guided surgery has, therefore, been suggested to facilitate parathyroid exploration. This was recently shown to be particularly true in the reoperative neck [22]. Although the same group advocated radioguided surgery for primary parathyroid surgery as well [23], this was contradicted in a recent report by Bonjer et al. [24].

Regardless of the imaging modalities advocated, several other investigators have proposed less invasive strategies as alternative to CNE. Most have focussed on unilateral neck exploration [5 14]. Because this still requires the dissection of normal parathyroids, such an approach will doubtlessly lack many of the advantages of MIA. Chapuis et al. have described a truly minimally invasive technique, performing ultrasound-guided adenomectomy under local anesthesia [3]. Although this was feasible in only approximately 40% of their patients, we believe that in selected patients direct adenomectomy as described in our study could eventually be carried out under local anesthesia as well. This was recently confirmed by Norman and Chheda [23], who used a direct approach under local anesthesia by reducing the dissection field using nuclear scintigraphy and perioperative localization with a hand-held probe. Alternatively, some surgeons have advocated endoscopy to perform a minimally invasive adenomectomy in selected patients [25]. Although conceptually elegant, this technique appears difficult to learn and certainly requires more operating time than the direct approach described here.

In conclusion, this study has shown that MIA is a safe and effective technique that may be anticipated to replace CNE in approximately 75% of patients undergoing surgical treatment of pHPT. Preoperative imaging should include a combination of ultrasound and CT scanning, including the possibility of cinevision. Perioperative measurement of PTH levels by rapid test methods will improve the surgical management of missed adenomas, permitting prompt CNE if MIA fails.

References

1 Van Heerden JA, Grant CS. Surgical treatment of primary hyperparathyroidism: an institutional perspective. World J Surg 1991; 15: 688-692

2 Ryan JA, Lee F. Effectiveness and safety of 100 consecutive parathyroidectomies. Am J Surg 1997; 173: 441-444

3 Chapuis Y, Icard P, Fulla Y et al. Parathyroid adenomectomy under local anesthesia with intraoperative monitoring of UcAMP and/or 1-84 PTH. World J Surg 1992; 16: 570-575

4 Van Vroonhoven TJMV, van Dalen A. Successful minimally invasive surgery in primary hyperparathyroidism after combined preoperative ultrasound and computed tomography imaging. J Int Med 1998; 243: 581-587

5 Lucas RJ, Welsh RJ, Glover JL. Unilateral neck exploration for primary hyperparathroidism. Arch Surg 1990; 125: 982-985

6 Irvin GL, Prudhomme DL, Deriso GT et al. A new approach to parathyroidectomy. Ann Surg 1994; 219: 574-581

7 Miller DL. Pre-operative localization and interventional treatment of parathyroid tumors: when and how? World J Surg 1991; 15: 706-715

8 Zmora O, Schachter PP, Heyman Z et al. Correct preoperative localization: does it permit a change in operative strategy for primary hyperparathyroidism? Surgery 1995; 118: 932-935

9 Smit PC, van Dalen A, van Vroonhoven TJMV. Strategy in asymptomatic and mildly symptomatic primary hyperparathyroidism, new arguments for the surgical option. Neth J Med 1998; 52: 95-99

10 Smit PC, Thijssen JHH, Borel Rinkes IHM, van Vroonhoven TJMV. Peroperative PTH testing: confirmation of successful surgical treatment of primary hyperparathyroidism. Ned Tijdschr Geneesk 1999 ; 143: 742-746

11 Bonjer HJ, Bruining HA, Birkenhager JC et al. Single and multigland disease in primary hyperparathyriodism: clinical follow-up, histopathology, and flow cytometric DNA analysis. World J Surg 1992; 16: 737-743

12 Juhlin C, Rastad J, Klareskog L et al. Parathyroid histology and cytology with monoclonal antibodies recognizing a calcium sensor of parathyroid cells. Am J Pathol 1989; 135: 321-328

13 Kaplan E, Yashiro T, Salti G. Primary hyperparathyroidism in the 1990s: choice of surgical procedures in this disease. Ann Surg 1992; 215: 300-317

14 Irvin GC, Deriso GT. A new practical intraoperative parathyroid assay. Am J Surg 1994; 168: 466-468

15 Michelangeli VP, Heyma P, Colman PG, Ebeling PR. Evaluation of a new, rapid and automated immunochemiluminometric assay for the measurement of serum intact parathyroid hormone. Ann Clin Biochem 1997; 34: 97-103

16 Bergenfelz A, Isakkson A, Lindslom P et al. Measurements of parathyroid hormone in patients with primary hyperparathyroidism undergoing first and reoperative surgery. Br J Surg 1998; 85: 1129-1132

17 Krubsack AJ, Wilson SD, Lawson TC et al. Prospective comparison of radionuclide, computed tomographic and sonographic localization of parathyroid tumors. World J Surg 1986; 10: 579-585

18 Roses DF, Sudarsky LA, Sanger J et al. The use of preoperative localization of adenomas of the parathyroid glands by thallium-technetium scintigraphy, high-resolution ultrasonography and computed tomography. Surg Gynecol Obstet 1989; 168: 99-106

19 Hasselgren PO, Fidler JP. Further evidence against the routine use of parathyroid ultrasonography prior to initial neck exploration for hyperparathyroidism. Am J Surg 1992; 164: 337-340

20 Mitchell BK, Merell RC, Kinder BK. Localization studies in patients with hyperparathyroidism. Surg Clin North Am 1995; 75: 483-498

21 Pattou F, Huglo D, Proye C. Radionuclide scanning in parathyroid disease. Br J Surg 1998; 85: 1605-1616

22 Norman J, Denham D. Minimally invasive radioguided parathyroidectomy in the reoperative neck. Surgery 1998; 124: 1088-1093

23 Norman J, Chheda H. Minimally invasive parathyroidectomy facilitated by intraoperative nuclear mapping. Surgery 1997; 122: 998-1004

24 Bonjer HJ, Bruining HA, Pols HA et al. 2-Methoxyisobutulisonitrile probe during parathyroid surgery: tool or gadget? World J Surg 1998; 22: 507-512

25 Miccoli P, Bendinelli C, Vignali E et al. Endoscopic parathyroidectomy; Report of an initial experience. Surgery 1998; 124: 1077-1080

Strategy in asymptomatic and mildly symptomatic primary hyperparathyroidism, new arguments for the surgical option

5

Smit PC, van Dalen A, van Vroonhoven TJMV. Strategy in asymptomatic and mildly symptomatic primary hyperparathyroidism, new arguments for the surgical option. The Netherlands Journal of Medicine 1998 ; 52 : 95 - 99

The widespread use of multichannel serum chemistry autoanalyzers has resulted in a sevenfold increase in the reported incidence of primary hyperparathyroidism (pHPT) [1]. Subsequently physicians have been increasingly confronted with the most common form of pHPT: an asymptomatic or mildly symptomatic disease characterized by mild chronic hypercalcemia with or without subtle symptoms such as fatigue and muscular weakness. It is estimated that approximately 80% of all the patients with pHPT fall into this category [2]. Today it can be calculated that pHPT develops in about 6000 patients each year in the Netherlands.

The serendipitous discovery of asymptomatic and mild pHPT has raised relevant questions about the advisability of treatment in these patients. At the National Institutes of Health (NIH) Consensus Development Conference on Diagnosis and Management of Asymptomatic pHPT in 1990, surgical treatment was advised along the guidelines given in **Table 1** [3]. One could wonder however, why operative treatment is not advised in more patients with pHPT, for surgery is the only curative treatment available, surgery is very successful (return to normocalcemia is achieved in up to 95-99% of cases in experienced hands), surgery has a low morbidity and even with a long follow-up the recurrence rate is very low [4]. Furthermore, after successful surgery the patient is saved repeated monitoring and long term follow-up and there is no chance of developing one of the more severe complications of hypercalcemia.

Table 1 Indications for surgical treatment in primary hyperparathyroidism according to the National Institutes of Health Consensus Statement 1990.

Markedly elevated serum calcium: 2.85 to 3.00 mmol/L (normal range 2.20 to 2.60 mmol/L)
History of an episode of life-threatening hypercalcemia
Reduced creatinine clearance: reduced by 30% compared with age-matched normal persons
Confirmed 24-hour urine calcium excretion > 10 mmol (normal range 2.5 to 7.5 mmol/24 hr)
Substantially reduced bone mass: more than two standard deviations below age-, gender-, and race-matched controls
In addition:
Patient requests surgery
Consistent follow-up is unlikely
Coexistent illness complicates management
Patient is below the age of 50 years

The standard operation for pHPT is a systematic bilateral neck exploration in which all four parathyroid glands are sought and when identified, the macroscopically enlarged glands are removed. It is understandable that there is some reservation towards this surgical option. After all, there is a discrepancy between the extent of the operation and incision versus the median size of the causative parathyroid adenoma weighing in general no more then 200-300 mg. Although surgical exploration is attended with a low morbidity, when complications do occur they are serious. There is a small risk of permanent hypoparathyroidism (ranges between virtually zero and four percent) and damage to the recurrent laryngeal nerve leading to hoarseness and a reduced voice volume in less than one percent of the cases [2]. Also persistent hypercalcemia postoperatively, signaling a failure of the operation, has to be considered as a complication [5].

It has to be realized that pHPT is a solitary gland disease in at least 85-90% of the patients, meaning that in the majority of patients only one enlarged gland is causing the disease and consequently that removal of that one enlarged gland cures the patient. Why then is an extensive bilateral neck exploration still the gold standard when surgery is indicated ? The reason lies in the fact that preoperative localisatory techniques have up till now not yielded satisfactory results in attempts to replace the systematic bilateral neck exploration with a less extensive operation, although unilateral operations have been advocated by some [6 7 8]. The overall sensitivity of techniques like ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), thallium-201/technetium-99m scintigraphy and technetium-99m sestamibi imaging ranges from 40 to 90%, with specificity reported from 65 to 95% (**Table 2**) [9]. Ultrasonography is undoubtedly operator-

Table 2 Sensitivities and specificities of parathyroid imaging in patients without previous neck surgery.

	sensitivity %	specificity %	references
Ultrasonography	34-92	75-96	9 11 12 17 18
Computed Tomography	41-86	62-94	9 11 12 18
Magnetic Resonance Imaging	57-90	75-91	9 12 17 18
Thallium 201/technetium-99m scintigraphy	25-74	68-93	9 11 12 17 18
Technetium-99m sestamibi iodine 123 imaging	60-88	97-100	19 20 21 22

dependent whereas, not surprisingly, the sensitivity of all procedures declines when the weight of the enlarged gland drops below 500 mg [9 10 11 12]. These techniques are also less accurate after previous neck surgery. Combining tests has yielded somewhat better results: up to 87% using scintigraphy in combination with US [8]. The combination of three or more techniques has not increased the success rate [10].
In general the results of preoperative imaging have not been good enough for a substantial change in surgical policy. According to most authorities a bilateral neck exploration is still the procedure of first choice when surgical treatment is indicated [4 13 14]. In this respect one of the most cited remarks is that of the prominent American radiologist Doppman 'The only localizing modality required in the patient who has not had any previous neck surgery is to localize an experienced parathyroid surgeon'.

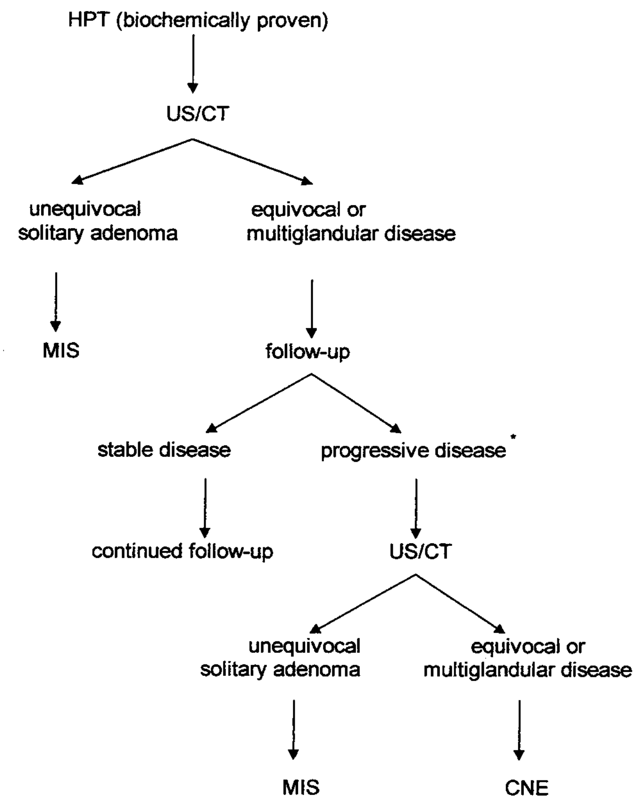
So, seven years after the NIH consensus meeting, nothing much seems to have changed. The indication to operate in patients with pHPT is, in the group fulfilling the NIH criteria and/or suffering from major symptoms such as nefrolithiasis and severe bone-pain, no matter of debate. For the majority of patients, that is the group which is asymptomatic or only mildly symptomatic, most physicians understandably still prefer a conservative attitude.
However during these years changes have occurred as well in surgery as in radiology and these changes might be relevant for patients with pHPT. The most prominent change in surgery more recently has been the development and implementation of minimally invasive techniques best exemplified by procedures such as laparoscopic cholecystectomy and laparoscopic inguinal hernia repair. This in turn has led more and more patients to request the least invasive technique possible, also in other areas of surgery. Progress in technology has greatly affected radiological imaging. This improvement contributes considerably to the imaging quality of the radiological techniques as US and CT, creating new possibilities for more reliable localisatory procedures in pHPT.
Looking for a less invasive procedure in parathyroid surgery, encouraged by the improvement of the radiological techniques and aware of the very high incidence of solitary adenoma in pHPT, the subjoined hypothesis was born. If it would be possible to localize the parathyroid adenoma preoperatively with high accuracy, an adenomectomy by a local procedure instead of the conventional neck exploration would be a potential option, resulting in less morbidity, reduction of operation and admission time, and leaving a surgical scar of about 1.5 cm instead of at least 10 cm length.
Using Doppler assisted US and spiral CT for preoperative parathyroid imaging the feasibility of a minimally invasive approach was tested by us originally in 15 symptomatic patients [15]. From the successful results it could be calculated that minimally invasive surgery would probably suffice in at least 70% of patients with pHPT,

so that conventional neck exploration can be avoided. These good initial results were further corroborated in a subsequent large prospective evaluation study including all consecutive patients who presented with an indication for operative treatment [16]. This series again proved the correctness of the original hypothesis. A total of 66 patients (54 female, 12 male) with a median age of 60 years and a median serum calcium of 2.90 mmol/L (2.55-3.60) were studied. Fifty-one of these patients underwent a minimally invasive approach which was successful in 49. In two patients conversion to a conventional neck exploration -in the same operative session- was necessary. A conventional neck exploration was primarily carried out in the other 15 patients because of equivocal results of preoperative imaging. The median operation time in the minimally invasive group was 15 minutes (10-35), that in the group which underwent the conventional neck exploration was 75 minutes (60-120). All 66 patients became normocalcemic postoperatively. Except for one patient who suffered a transient unilateral vocal cord paralysis no complications were registered. Overall the combination of preoperative Doppler US and spiral CT-scanning made a successful minimally invasive approach of pHPT possible in 74% (49/66) of patients.

The data presented above leave us in no doubt that minimally invasive surgery definitively has entered the treatment of pHPT. This certainly applies to the patients with symptomatic disease, but it could well have consequences also for the large group of patients with asymptomatic or only mildly symptomatic pHPT. Suppose a patient with asymptomatic or only mildly symptomatic pHPT undergoes parathyroid imaging, preferably by US and CT (based on our personal favourable experience), and imaging shows a definite adenoma suited for the minimally invasive approach then this patient could be definitively cured by a small operation and with a low chance of recurrence of disease this obviates the need for frequent out-patient follow-up, and for repeated blood testing and prevents any anxiety that symptoms will occur or will worsen.

In other words, experience with the minimally invasive approach of pHPT in symptomatic patients has given us new arguments for the surgical option in asymptomatic or mildly symptomatic pHPT patients. We therefore tentatively propose a new strategy. If a patient presents with a biochemically proven asymptomatic or mildly symptomatic pHPT decision-making according to the following algorithm is advised (**Table 3**). Localization of the enlarged gland should be attempted by means of doppler US and spiral CT. The examinations should be performed systematically under guidance of a dedicated radiologist and the results discussed with the surgeon in charge. When the test results unequivocally indicate a solitary adenoma the patient is advised to undergo a minimally invasive procedure. When the test results are equivocal or indicate the possibility of multiglandular disease a conservative policy is advocated. When the disease should progress in time or the patient develops major symptoms and/or fulfils the NIH-guidelines, parathyroid

Table 3 Algorithm in asymptomatic/mildly symptomatic pHPT.



pHPT	primary hyperparathyroidism
US	doppler assisted ultrasonography
CT	spiral computed tomography
MIS	minimally invasive surgery
CNE	conventional neck exploration

*progressive disease is defined as the development of signs according the NIH-criteria which were previously absent and/or the development of major symptoms.

imaging procedures should be repeated preceding the then indicated operative treatment.

Implementation of such a strategy could be of considerable benefit to a substantial number of patients with asymptomatic or only mildly symptomatic primary hyperparathyroidism.

References

1 Heath H III, Hodgson SF, Kennedy MA. Primary hyperparathyroidism: incidence, morbidity, and potential economic impact in a community. N Eng J Med 1980; 302: 189-193
2 Chan FKW, Koberle LMC, Thys-Jacobs S, Bilezikian JP. Differential diagnosis, causes, and management of hypercalcemia. Curr Probl Surg 1997; 34: 445-524
3 Consensus Development Conference Panel. Diagnosis and Management of Asymptomatic primary hyperparathyroidism: Consensus Development Conference Statement. Ann Int Med 1991; 114: 593-597
4 Van Heerden JA, Grant CS. Surgical treatment of primary hyperparathyroidism: an institutional perspective. World J Surg 1991; 15: 688-692
5 Irvin GL, Dembrow VD, Prudhomme DL. Operative monitoring of parathyroid gland hyperfunctioning. Am J Surg 1991; 162: 299-302
6 Lucas RJ, Welsh RJ, Glover JL. Unilateral neck exploration for primary hyperparathyroidism. Arch Surg 1990; 125: 982-984
7 Irvin GL, Prudhomme DL, Deriso GT, Sfakianakis G, Chanderlapaty SKC. A new approach to parathyroidectomy. Ann Surg 1994; 219: 574-581
8 Ryan JA, Eisenberg B, Pado KM, Lee F. Efficacy of selective unilateral exploration in hyperparathyroidism based on localization tests. Arch Surg 1997; 132: 886-890
9 Miller DL. Pre-operative localization and interventional treatment of parathyroid tumors: when and how ? World J Surg 1991; 15: 706-715
10 Winzelberg GG, Hydovitz JD, O'Hara KR, et al. Parathyroid adenomas evaluated by Th-201/Tc-99m pertechnetate substraction scintigraphy and high-resolution ultrasonography. Radiology 1985; 155: 231-235
11 Roses DF, Sudarsky LA, Sanger J, et al. The use of operative localization of adenomas of the parathyroid glands by thallium-technetium scintigraphy, high-resolution ultrasonography and computed tomography. Surg Gynecol Obstet 1989; 168: 99-106
12 Krubsack AJ, Wilson SD, Lawson TC, et al. Prospective comparison of radionuclide, computed tomographic and sonographic localization of parathyroid tumors. World J Surg 1986; 10: 579-585
13 Proye CAG, Carnaille B, Bizard JP, Quievreux JL, Leconte-Houcke M. Multiglandulair disease in seemingly sporadic primary hyperparathyroidism revisited: where are we in the 1990s ? A plea against unilateral parathyroid exploration. Surgery 1992; 112: 1118-1122
14 Zmora O, Schachter PP, Heyman Z, et al. Correct preoperative localization: does it permit a change in operative strategy for primary hyperparathyroidism ? Surgery 1995; 118: 932-935
15 Van Vroonhoven TJMV, Van Dalen A, Koppeschaar HP, Duursma SA. Favourable results on minimally invasive surgery in the treatment of primary hyperparathyroidism. Ned T Geneesk 1996; 140: 304-308

16 Van Vroonhoven TJMV, Van Dalen A. Successful minimally invasive surgery in primary hyperparathyroidism after combined preoperative ultrasound and computed tomography imaging. J Int Med 1998; 243: 581-587

17 Attie JN, Khan A, Rumancik WM, et al. Preoperative localization of parathyroid adenomas. Am J Surg 1988; 156: 323-326

18 Erdman WA, Breslau NA, Weinreb JC, et al. Noninvasive localization of parathyroid adenomas: a comparison of x-ray computerized tomography, ultrasound, scintigraphy and MRI. Magn Reson Imaging 1989; 7: 189-194

19 Chapuis Y, Fulla Y, Bonnichon P, et al. Values of ultrasonography, sestamibi scintigraphy, and intraoperative measurement of 1-84 PTH for unilateral neck exploration of primary hyperparathyroidism. World J Surg 1996; 20: 835-840

20 Wei JP, Burke GJ, Mansberger AR. Preoperative imaging of abnormal parathyroid glands in patients with hyperparathyroid disease using combination Tc 99-m pertechnetate and Tc 99-m sestamibi radionuclide scans. Ann Surg 1994; 219: 568-573

21 Caixàs A, Bernà L, Hernández A, et al. Efficacy of preoperative diagnostic imaging localization of technetium 99-m sestamibi scintigraphy in hyperparathyroidism. Surg 1997; 121: 535-541

22 Shen W, Sabanci U, Morita ET, et al. Sestamibi scanning is inadequate for directing unilateral neck exploration for first-time parathyroidectomy. Arch Surg 1997; 132: 969-974

Minimally invasive surgery of solitary parathyroid adenomas in patients with primary hyperparathyroidism;

Role of ultrasonography with supplemental computed tomography

6

Accepted for publication in Radiology as Van Dalen A, Smit PC, van Vroonhoven TJMV, Burger H, de Lange EE. Minimally invasive surgery of solitary parathyroid adenomas in patients with primary hyperparathyroidism; Role of ultrasonography with supplemental computed tomography.

Abstract

Purpose To determine the role of ultrasound (US) with supplemental computed tomography (CT) in patients with primary hyperparathyroidism (pHPT) to undergo minimally invasive surgery (MIS) instead of conventional neck exploration.

Materials and methods US and CT were performed in 61 consecutive patients with pHPT (part I) to identify and localize solitary adenomas for resection by MIS and to provide a surgical roadmap. In part II, involving 33 consecutive patients, CT was performed only when no solitary adenoma was identified with US, or for roadmap information. MIS was considered successful when serum calcium levels normalized and remained stable.

Results In part I, 46 definite solitary adenomas were found by US and two additional ones by CT. MIS was successful in 45 patients and failed once. In part II, US identified 23 solitary adenomas and CT found one. MIS was successful in 22 patients and failed in two. Combined results of 94 patients demonstrated successful MIS in 67 (71%), with 64 of them selected by US alone (95% CI: 61-80).The sensitivity of US in diagnosing solitary adenomas was 78% (95% CI: 67-86) with a positive predictive value of 96% (95% CI: 88-99).

Conclusion US evaluation of patients with pHPT allowed successful selection for MIS in more than two thirds of cases, with additional CT being chiefly useful for surgical road-mapping.

Introduction

Primary hyperparathyroidism (pHPT) is a relatively uncommon disease in adults with an estimated prevalence of 1 : 700 in the United States [1]. Women, particularly postmenopausal, are affected 2 to 3 times more frequently than men [2]. Clinical manifestations of pHPT include renal calculi, gastric ulcers, bone cysts and mental depression. Its diagnosis is based on elevated serum calcium and parathyroid hormone levels. In the vast majority (approximately 85%) of patients, a solitary parathyroid adenoma is the cause of the disease [3 4 5]. Multiglandular involvement, either caused by multiple adenomas (4%) or diffuse hyperplasia (10%), is much less common [4]. Rare causes of pHPT are parathyroid cyst and carcinoma.

The common treatment of pHPT is conventional neck exploration (CNE) [6]. With this procedure, the neck is explored in order to identify all parathyroid glands and to remove the enlarged ones. CNE is a time consuming and surgically demanding procedure because of the many vulnerable structures of the neck that need to be explored to allow identification of the parathyroid glands. Nevertheless, in experienced hands, CNE is curative in 95% of cases with few reported complications [6 7 8].

Recently, we introduced minimally invasive surgery (MIS) by use of US and CT imaging to treat patients in whom the disease is caused by a solitary adenoma, and in this earlier report, which included 61 patients of the current study, we highlighted the clinical aspects of this method [9]. During the MIS procedure, the surgeon, guided by an imaging-based roadmap, carefully approaches the lesion through a small incision in the skin and removes it with minimal damage to the vulnerable structures of the neck. Advantages of MIS compared to CNE include reduction in operation time and hospital stay with subsequent decreased costs, improved cosmetic results, and restriction of postoperative fibrosis to the immediate area of the removed gland, facilitating re-operation in case of recurrence of disease [10].

The typical adenoma is small, usually not palpable because its consistency is equal to that of fat, and is often hidden among the structures of the neck. Consequently, a high accuracy is required in diagnosing and localizing the solitary lesion. In addition, accurate determination of its relationship with the surrounding structures is needed in order to perform MIS successfully.

The purpose of the current study was to investigate prospectively the role of ultrasonography (US) as the primary imaging modality for identification and localization of parathyroid adenomas in patients with pHPT to undergo MIS. As the surgical technique was relatively new when we initiated this study and we were uncertain about the full potential of US in facilitating the surgery, we used computed tomography (CT) as a supplemental test to increase confidence in lesion diagnosis and to provide an operator-independent roadmap for the surgeon.

Materials and methods

Overall design

The study population consisted of consecutive patients admitted to our institution who were scheduled for surgical treatment of clinically proven pHPT, i.e. a blood serum parathyroid hormone level higher than 8 pmol/L and/or a serum calcium level higher than 2.60 mmol/L. Ninety-four patients with pHPT were enrolled, 21 of them were men and 73 women, with a mean age of 58 (range 17-84). The median serum calcium level was 2.82 mmol/L (normal 2.20-2.60 mmol/L; range 2.42-3.60 mmol/L), the median serum parathormone was 12.2 pmol/L (normal <8 pmol/L in normocalcemic state; range 4.9-234.0 pmol/L). One or more manifestations of the disease were present in 40 (43%) patients; 21 had renal stones, 20 suffered from malaise/fatigue and 10 patients from bone/joint pain.

Two distinct diagnostic strategies were followed. In the first (part I, 61 patients), performed from October 1994 through April 1997, all patients underwent both US and CT imaging of the neck. In the second (part II, 33 patients), performed from May 1997 through April 1998, all patients underwent US, and supplemental CT was performed only when no solitary adenoma was identified by US or when requested by the surgeon for additional road-mapping. Eighty-nine of the 94 US examinations were performed and interpreted by one radiologist (AvD). This radiologist also interpreted the US findings of the remaining five patients whose examinations were performed by an experienced sonographer. In all cases the US findings were interpreted without knowledge of any prior imaging studies, if present. All CT images were interpreted by the same radiologist with knowledge of the US findings, and the final diagnosis was based on the combined results. When the final preoperative diagnosis of a definite solitary adenoma was made, the patient was scheduled for MIS, and in all other cases CNE was performed. The study was approved by the Institutional Review Board, and informed patient consent was obtained in all cases. All patients who were scheduled for MIS had a repeat US examination immediately prior to the operation with the neck extended in the position in which surgery was going to be performed. The previously diagnosed solitary adenoma was then localized again in the presence of the surgeon, the surgical approach assessed and the optimal incision site marked on the skin of the patient.

Ultrasound imaging

The equipment used were real time units with 4-7 mHz and 5-10 mHz transducers (HDI 900 and 3000, Advanced Technical Laboratories, Bothel WA, USA). Examination was performed with the patient in supine position and the neck extended. The area from the carotid bifurcation to the deepest accessible part of the mediastinum was scanned in longitudinal and transverse planes. Graded compression was used to improve visualization of the deep paratracheal and para-esophageal areas, and, in case of doubt, to differentiate between an intra- or extrathyroidal location of a lesion. When a possible parathyroid lesion was identified, color-Doppler was applied to determine the presence of vascularity of the lesion and/or to identify a vascular pedicle favoring the diagnosis of a parathyroid adenoma. Lesion mobility during swallowing and/or deep breathing was also observed to allow differentiation from structures such as para-carotid cervical lymph nodes or the longus colli muscle. The thyroid gland was also evaluated and assessed for the presence of disease. The initial US examination required approximately 15 minutes and the preoperative repeat examination about 5 minutes.

Spiral Computed Tomography imaging

Contrast-enhanced CT scanning was performed with the patient in supine position and the neck in slight extension with the shoulders pulled down as much as possible. Ninety mL of non-ionic contrast medium (Isovist, Schering M, Berlin, Germany) were given intravenously with a rate of 2 mL/sec. Imaging was initiated 25 sec. after the beginning of the administration of the contrast medium. In a single breath-hold the volume from the level of the mandibular angle to that of the aortic root was scanned. A table speed of 5 mm/sec. and a slice thickness of 5 mm with a gantry rotation time of 1 sec. were applied with a reconstruction index of 3 mm. The obtained images were evaluated on hard copy and in cine loop using a dedicated computer workstation (EasyVision workstation; Release 2.1, Philips Medical Systems, Best, The Netherlands).

Grading of adenomas by Ultrasound and Computed Tomography

Ultrasound: The normal parathyroid glands are oval or bean-shaped and measure on average 6 mm in length with a mean weight of 40 mg. They contain a considerable amount of stromal fat [11] and are generally not visualized with current US equipment [12]. The US diagnosis of a typical 'definite' adenoma was made when a lesion was visualized with a homogeneous hypo-echoic reflection pattern relative to thyroid tissue (**Figure 1**) and showing the following characteristics. Typically, the shape varied from round/oval to elongated with an alignment in a craniocaudad orientation and a diameter of at least of 8 mm when round or up to 3 cm long when elongated [5 13 14 15]. In addition, the typical adenoma was located closely to the

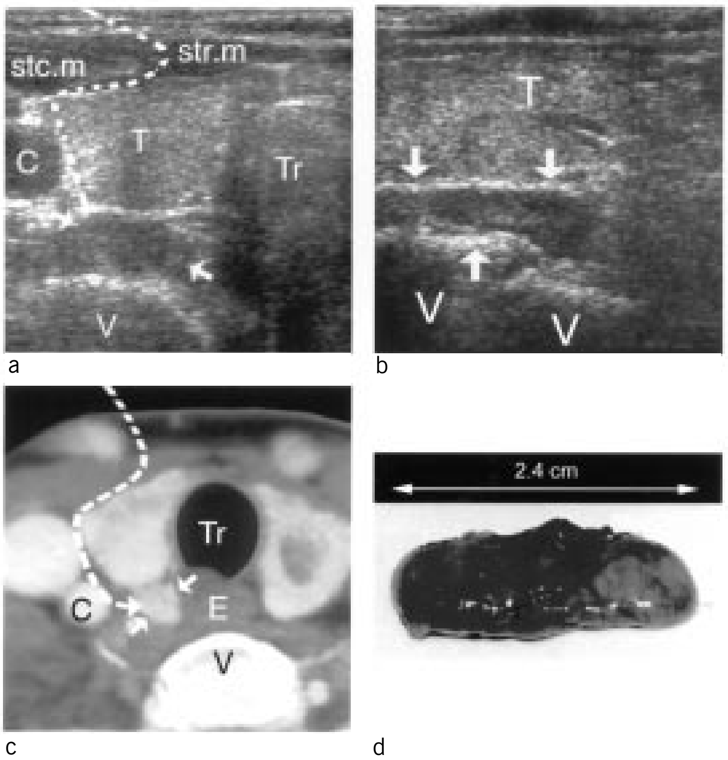


Figure 1 *Patient with a solitary adenoma, superior type.*

(a) *Transverse US image of the neck demonstrating the adenoma (between arrows) as a hypoechoic lesion behind the right thyroid lobe, allowing the diagnosis of a definite adenoma. The surgical approach is drawn with a dotted line.*
(b) *Longitudinal US image showing the adenoma as an elongated mass (between arrows) located behind the thyroid, consistent with a 'superior type' adenoma.*
(c) *Transverse CT image of the neck at the same anatomic level as figure 1a showing the adenoma (between arrows) and surrounding structures. The surgical approach is drawn with dotted line.*
(d) *Surgical specimen of the adenoma. Weight 705 mg.*
Note: T = thyroid, Tr = trachea, C = carotid artery, V = vertebral body, E = esophagus, stc.m = sternocleidomastoid muscle, str.m strap muscles.

thyroid gland, or more caudad in the paratracheal or para-esophageal space. Essential for the diagnosis of a parathyroid adenoma was that the lesion retained its relationship with the thyroid gland during swallowing and deep breathing and did not show a central hilum.
Furthermore, any oval, elongated or lobulated lesion in the same location and with

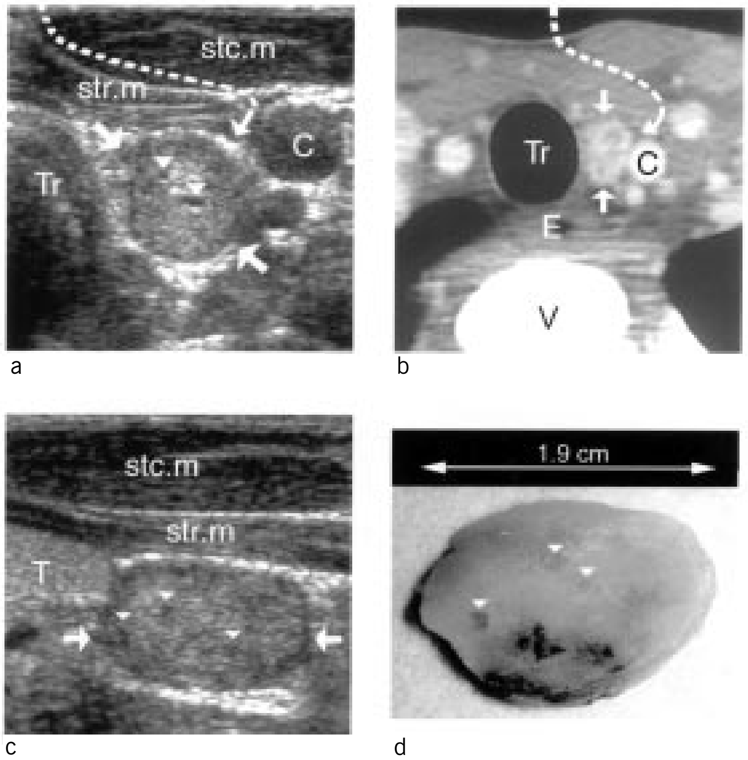


Figure 2 *Patient with a solitary adenoma, inferior type.*

(a) Transverse US image demonstrating the adenoma as an oval echogenic lesion (arrows) with small cystic changes (arrow heads). The surgical approach is drawn with dotted line.
(b) Transverse CT image corresponding to figure 2a demonstrating the adenoma (arrows) and the surgical approach (dotted line).
(c) Longitudinal US section showing that the adenoma (arrows) is located just caudad to the thyroid gland and close to the strap muscles, corresponding with an 'inferior-type' adenoma. Few small cysts (arrow heads) are present.
(d) Surgical specimen of the adenoma demonstrating the multiple small cysts (arrow heads). Weight 1287 mg.
Note: T = thyroid, Tr = trachea, C = carotid artery, V = vertebral body, E = esophagus, stc.m = sternocleidomastoid muscle, str.m strap muscles.

the same mobility, but with an increased and/or irregular reflection pattern, cystic changes (**Figure 2**) and/or calcifications representing degeneration [13 14] and measuring from 1-2 cm to approximately 5 cm in length, was also considered a definite adenoma. A subcapsular, intrathyroidal lesion with the characteristics of a parathy-

roid adenoma was considered a definite parathyroid adenoma when the thyroid was otherwise normal and when there was no evidence of an adenoma elsewhere. A poorly visualized lesion with localization and movement at swallowing suggestive of adenoma was also considered a definite adenoma when the lesion showed clear vascularity by color Doppler (**Figure 3**).
A lesion was considered an 'equivocal' adenoma in case its characteristics did not completely fulfill the criteria given above. A lesion was diagnosed as no adenoma when its mobility during swallowing was not related to that of the thyroid unless an aberrant location e.g. in the carotid sheath was considered or when an evident central hilum was visualized and also the shape, size and reflection pattern were compatible with a lymph node. A patient was considered to have a definite 'solitary' adenoma when a definite adenoma as described earlier was the only identified lesion. In all other instances, i.e. when an equivocal solitary lesion, definite or equivocal multiple lesions, or no lesions were found, the diagnosis of 'no definite solitary adenoma' was made. When the solitary adenoma was located posterior to the thyroid lobe near the mid portion, it was called a 'superior type' adenoma (**Figure 1**). It was called an 'inferior type' when it was located near the lower pole of a thyroid lobe or inferior to it and having, at least in part, a close relationship with the anterior muscular wall of the neck (**Figure 2**). Any other location was considered 'aberrant'.

Computed Tomography: The images were analyzed with knowledge of US findings. In a case of a definite adenoma by US the diagnosis was not changed when the CT and US findings were compatible; otherwise the final diagnosis was equivocal adenoma. Criteria were that either the adenoma was visualized by CT as a contrast-enhancing lesion in the same location and with the same size as seen with US or, in case of a close relationship with the thyroid gland by US, the lesion was only recognized as a local bulge of the contour of the thyroid at the same location as seen with US.
When a lesion was diagnosed by US as an equivocal adenoma because of poor visualization, it was considered a definite adenoma when it was visualized by CT as a contrast enhancing lesion in the same location and with the same size as seen with US. In case of a lesion, well visualized by US but diagnosed as an equivocal adenoma because it did not fulfill the other criteria as described earlier, the US diagnosis was not changed by the CT findings.

When by CT an enhancing lesion with the size and location compatible with a parathyroid adenoma was found which was not visualized by US, it was considered a definite adenoma only if it was located in an area not well accessible to US examination, such as the deep para-esophageal and mediastinal regions; otherwise the lesion was considered an equivocal adenoma.

Surgical procedure, histopathology and follow-up

Guided by the imaging-based ‘road map’, MIS was begun with a 2-cm, transverse incision at the medial border of the sternocleidomastoid muscle at the site of the skin marking. After lateral mobilization of the muscle, internal jugular vein and common carotid artery and medial mobilization of the strap muscles and thyroid gland, the tracheo-esophageal groove was entered and the enlarged gland was identified and removed (**Figure 1**). If during MIS no lesion could be identified, the surgery was converted to CNE. Surgery was qualified as successful when the serum calcium levels normalized within 24 hours and remained stable for at least 6 months. The surgical specimens were weighted in the pathology department, and histopathological examination was performed by the pathologist to assess the presence of parathyroid tissue. The lesions were considered to represent adenoma when at histological evaluation parathyroid tissue was found. Histological differentiation between adenoma and hyperplasia was not made in our institution [16].

Statistical analysis

The data were analyzed statistically using two different approaches. The first analyses were performed while considering the *patients as the units of analysis.* As only definite solitary adenomas were considered eligible for MIS, the imaging results were categorized as patients with the preoperative diagnosis ‘solitary adenoma’ or ‘no solitary adenoma’. In other words, the imaging was used as a screening test yielding either ‘solitary adenoma - eligible for MIS’ or ‘no solitary adenoma - not eligible for MIS’. To obtain sensitivity, specificity and predictive values of this screening test, a gold standard test indicating whether a patient in reality was suitable for MIS, is required. In this study, the latter can only be established with confidence after surgery and follow-up. Therefore, the final diagnosis serves as the gold standard in this study. The final diagnosis was made on the basis of the findings during surgery combined with the course of post-surgical serum calcium levels. If at surgery a single adenoma was removed and calcium levels normalized and remained stable as described earlier, the final diagnosis was ‘solitary adenoma’. In all other cases, the final diagnosis was ‘no solitary adenoma’. Using this approach, sensitivity of US denotes, among patients with a final diagnosis of solitary adenoma, the probability of a US diagnosis of a solitary adenoma at the same location as observed at surgery. The positive predictive value of US denotes, among patients with a solitary adenoma on US, the probability of a final diagnosis of solitary adenoma at the predicted location. The negative predictive value denotes, among patients with no solitary adenoma on US, the probability of a final diagnosis of no solitary adenoma. Specificity denotes, among patients with a final diagnosis of no solitary adenoma, the probability of no solitary adenoma on US. All probabilities from this analysis are presented as percentages with exact binomial 95% confidence intervals [17].

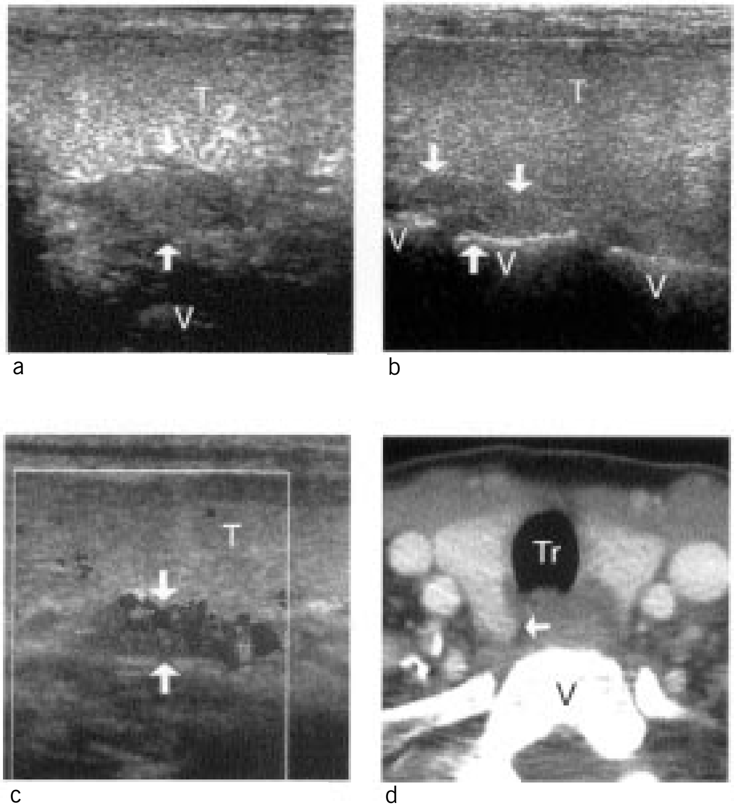


Figure 3 *Patient with a solitary adenoma, superior type.*

(a) Transverse US section shows ill-defined hypoechoic lesion (arrows) behind the right thyroid gland indicative of an 'equivocal' adenoma.

(b) Longitudinal section demonstrates again poor visualization of the lesion (arrows) which is compressed between thyroid and cervical spine.

(c) Transverse color Doppler US image at the same level as figure 3a showing extensive vascularization of the lesion, allowing diagnosis of a 'definite' adenoma.

(d) Transverse CT section showing the adenoma only as enlargement of the posterior aspect of the right thyroid lobe (arrow), due to its close relation to the thyroid and the identical enhancement.

Note: T = thyroid, Tr = trachea, C = carotid artery, V = vertebral body, E = esophagus.

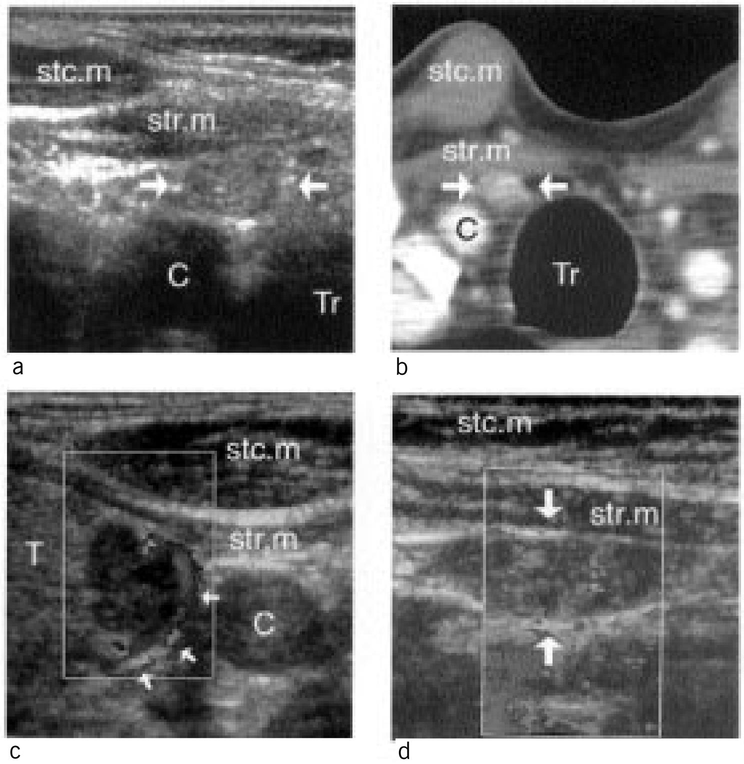


Figure 4 *Patient with incorrectly diagnosed solitary adenoma.*

(a) Transverse US image at level caudad to thyroid gland shows a moderately echogenic lesion (arrows) between the right carotid artery and the anterior muscular wall of the neck. The lesion was believed to be a solitary parathyroid adenoma.

(b) Transverse CT image at same level as 4a showing the same lesion (arrows), which was removed by MIS. Histopathologic examination of the specimen revealed only thyroid tissue.

(c) Transverse US section of the neck showing the solitary parathyroid adenoma found at subsequent CNE. The lesion is located subcapsularly in the thyroid gland and was believed to be a thyroid nodule at initial US examination. Doppler US shows the presence of a vascular pedicle (arrows).

(d) Longitudinal US section of the adenoma showing the oval shape but with rather sharp edges probably caused by the subcapsular position. In retrospect, these edges favor the diagnosis of a parathyroid adenoma above a thyroid nodule.

Note: T = thyroid, Tr = trachea, C = carotid artery, stc.m = sternocleidomastoid muscle, str.m strap muscles.

Second, we carried out analyses with *adenomas as units of analysis.* Because in this situation the number of no solitary adenoma diagnoses (both on ultrasound and at surgery) is undefined, only sensitivity and positive predictive value were calculated. Using this approach, the sensitivity denotes the probability that an adenoma found at surgery had also been identified at that site by US, and the positive predictive value is defined as the probability that an adenoma identified by ultrasound was present at surgery at the same location. As in this analysis the observations may not be independent within patients, confidence limits were omitted.

Results

The results of US, CT and surgery evaluation for both series are given in **Table 1**. In part I there were 61 patients; in 46 of those a definite solitary adenoma was diagnosed by US and the diagnosis was not changed by CT. In the remaining 15, CT changed the US diagnosis to a definite solitary adenoma in two cases. In one of them, CT changed the initial US diagnosis of equivocal to a definite solitary adenoma. In the other one, in whom no lesion was seen by US, CT identified a solitary adenoma in a deep paratracheal/mediastinal location (this lesion was later visualized, with knowledge of the CT findings, on the repeat US examination performed immediately before surgery). Thus, in part I there were 48 patients with the final diagnosis of a definite solitary adenoma. All underwent MIS except for one patient who underwent primary CNE because the MIS procedure was considered surgically impossible due to the presence of extensive multinodular goiter and resulting deep location of the lesion demonstrated by imaging. Of the 47 patients undergoing MIS, surgery was converted to CNE in one because during MIS the lesion could not be found due to extensive fibrosis in the operation area caused by prior thyroiditis. In the remaining 46, MIS was completed without surgical complications. Serum calcium levels normalized in 45 of these, resulting in a 98% success rate of the MIS procedure. Calcium levels did not normalize in one of the 46 patients, and histological examination of the specimen in this case revealed normal thyroid tissue without parathyroid components. In retrospect, the lesion that was diagnosed as a definite solitary adenoma by US and confirmed by CT, appeared to be an accessory thyroid gland, located two cm inferior to the right thyroid lobe (**Figure 4a,b**). CNE performed two days later revealed a small (274 mg) intrathyroidal parathyroid adenoma located subcapsular in the left lobe (**Figure 4c,d**). In another patient undergoing successful MIS, the visualized lesion proved to consist of two abutting adenomas rather than one solitary lesion, and the final postoperative diagnosis in this case was therefore multiple adenomas.

Table 1 Results of part I (n=61), part II (n=33) and combined results (n=94): Imaging diagnosis, type of surgery, failures and final findings.

	Imaging Diagnosis		Type Surgery		Failures	Final findings	
	US	combined US and CT	MIS	primary CNE		solitary	no solitary (multiple)
Part I							
Definite solitary adenoma	46	48	46+1*	1	1	47	1
No definite solitary adenoma	15	13	-	13	-	9	4
Total (patients)	61	61	46+1*	14	1	56	5
Part II							
Definite solitary adenoma	23	24	24	0	2	23	1
No definite solitary adenoma	10	9	-	9	1	6	3
Total (patients)	33	33	24	9	3	29	4
Combined results							
Definite solitary adenoma	69	72	71	1	3	70	2
No definite solitary adenoma	25	22	-	22	1	15	7
Total (patients)	94	94	70+1*	23	4	85	9

* Converted to CNE.

In part II there were 33 patients. In 23 of these a definite solitary lesion was diagnosed by US and they were directly scheduled for MIS. In the remaining 10, CT was subsequently performed which identified only one additional solitary adenoma in a deep para-esophageal location. Thus, in this series there were 24 patients with a solitary adenoma who all underwent primary MIS. In no case the operation was converted to CNE, and in all the removed lesion proved to contain parathyroid tissue at histopathological examination. In two of the 24 patients, however, serum calcium levels did not normalize following MIS. On subsequent CNE, a large (900 mg) second adenoma was found in one patient at the same location at which initially a small (230 mg) adenoma was removed during MIS. In this case only the large adenoma had been identified by imaging. In the other one, CNE revealed a large part of an adenoma at the same location where during prior MIS fragments of an adenoma were removed with total weight of 1,020 mg. In this case a much larger lesion (44x22x11 mm with estimated weight of 6,000 mg) had been diagnosed by the initial US. Thus, 22 of the 24 MIS procedures were successful resulting in a 92% success rate. In 6 of the 23 cases additional CT was performed at request of the surgeons, particularly by one who was new on the team and who had therefore less experience with the US-guided MIS procedure. In these patients, the CT scans were used exclusively for road-mapping in case of a deep para-esophageal location of the adenoma by US [3], severe enlargement of the thyroid due to goiter (2), or when there was an extremely large parathyroid adenoma diagnosed by US (n=1, weight of the specimen 16.010 mg). However, in these cases CT findings were not used for lesion diagnosis.

In part I and II combined, 69 definite solitary adenomas were diagnosed by US, in three of these the diagnosis was incorrect. Of the 66 solitary adenomas correctly diagnosed by US, 34 were in a 'superior' location, 27 were 'inferior' and 5 had an 'aberrant' location (intrathyroidal (n=1), para-esophageal (n=3) and cranial to the thyroid (n=1).

Histopathological results

At histopathological examination parathyroid tissue was identified in all 107 surgical specimens with exception of one, where only normal thyroid tissue was found. The median weight of the parathyroid specimens was 610 mg (range 90 -16,020 mg).

Statistical results

The results of the combined parts I and II in selecting patients with a solitary adenoma by US for MIS are depicted in **Table 2**. In total, there were 85 (90%) patients with a solitary adenoma according to the gold standard, i.e. the final operative results and change of the serum calcium levels. The sensitivity of US for diagnosing and localizing solitary parathyroid adenomas was 78% (66/85; 95%CI: 67-86) and the specificity also 78% (7/9; 95%CI: 40-97). The positive predictive value was 96% (66/69; 95%CI: 88-99) and the negative predictive value 28% (7/25; 95%CI: 12-49). In two of the three false positive cases there was multiglandular disease as described before, and in one there was a solitary adenoma which was not located at the predicted site.

In total, there were 106 adenomas in the 94 patients (85 with a solitary adenoma, and 21 adenomas in 9 patients with multiple lesions). The sensitivity of US for correctly diagnosing and localizing parathyroid adenomas was 74% (78/106); the positive predictive value was 98% (78/80). A false positive diagnosis of an adenoma was made in two patients. In one, the imaging-identified lesion proved to be aberrant thyroid tissue, and in the other, a small (8x7x3 mm) lesion identified by US, was not found at surgery.

Table 2 Results of US in correctly finding patients with a solitary parathyroid adenoma (part I and II combined).

	Results surgery		Total
Results US	present	not present	
Solitary adenoma	66	2+1*	69
No solitary adenoma	18	7	25
Total	84	9+1*	94

* one present, but not at predicted location.

Sensitivity	66/(84+1*)	78%
Positive predictive value	66/69	96%
Specificity	7/9	78%
Negative predictive value	7/25	28%

Discussion

The results of the first series of 61 patients with pHPT (part I) made it clear that, in more than two thirds (77%) of patients, successful MIS could be performed using the combined US-CT preoperative evaluation. In this series CT played only a limited role as additional diagnostic imaging modality, as there was no change in diagnosis in any of the 46 (75%) patients who harbored a definite US-diagnosed solitary adenoma, and it identified only two additional patients with such a lesion. These findings, combined with the increased confidence of the surgeon in the role of US, made us decide to initiate the second part of the study, in which CT was only used selectively. In this series (part II), CT only added one additional case for MIS.
The combined results of part I and II demonstrate that US is an excellent tool for selecting those patients with pHPT in whom successful MIS can be performed. In the 70 completed MIS procedures, three cases were selected by CT and thus 67 by US alone. Three of the 70 MIS procedures were unsuccessful, resulting in a 96% (67/70) success rate of the surgical procedure. This success rate for MIS is similar to that reported for primary CNE performed by experienced surgeons in patients who did not undergo preoperative imaging [6 7 8]. Thus, considering the results of the entire group of 94 patients, preoperative imaging was of major benefit to more than two thirds (71%) of our patients because they were able to undergo a limited, but equally successful operation for treatment of their pHPT instead of an extensive, complicated conventional surgical procedure.

It is well recognized, in case of ectopic adenomas with mediastinal or deep paratracheal and/or para-esophageal location, that US is of limited value because the lesions are generally inaccessible to the US beam; however, in these cases, they are usually well visualized by CT [3 5 13 14 18]. Nevertheless, in selecting patients for MIS, the added value of CT scanning was limited in our study because it identified only three additional definite solitary adenomas out of the entire group of 25 patients with ‘no solitary adenoma’ diagnosed by US. In two of these, the adenoma was located deeply in an area inaccessible to US, and in one the diagnosis of an equivocal lesion was changed to a definite solitary adenoma. Although in both cases of deep localization the adenoma was visualized at repeat US with knowledge of the CT findings, it is conceivable that visualization may be impossible at repeat US. In such a situation MIS could still be considered; however, the deep location of the lesion and the absence of preoperative localization of the adenoma and determination of the optimal incision site may make a surgical approach through a small opening in the skin very difficult, if not impossible.

In our study we used CT exclusively as an adjunctive test and we did not evaluate its role as primary imaging tool. However, in our experience, application of spiral

CT with cine loop presentation of images allows easy identification of a number of lesions and provides an excellent display of the visualized adenoma in its surrounding anatomical structures. Therefore, CT could potentially also be used as the primary test for selecting patients for MIS. However, the cost of CT is generally much higher than that of US, and the modality involves the use of ionizing radiation to a vulnerable area (thyroid gland) with associated risks [19]. For these reasons together with its good results we prefer to use US as the primary modality for selection of the patients for MIS. Nevertheless, in selected cases the surgeon may still want to have an additional CT for road mapping, as has been our experience, particularly in cases when the lesion is located deeply, or when the thyroid gland is enlarged.
Magnetic resonance (MR) imaging and scintigraphy have also been used for identification of parathyroid adenomas with results comparable to those of US and CT [4 20]. In our study we preferred to use CT as additional modality over MR imaging for reasons of availability and costs, and therefore the role of this modality in selecting patients for MIS was not determined. Conventional scintigraphy is, in our opinion, not well suited for selecting patients for our MIS procedure because of the relatively poor image resolution and anatomical information obtained. Recent studies have shown, however, that a minimally invasive surgical procedure is possible in cases where the uptake of the administered radiopharmacon is sufficient to allow localization of the parathyroid adenoma intra-operatively with a small gamma probe [21 22].

In one patient with two, contiguous adenomas simulating one lesion by imaging, MIS was successfully performed because during the surgery a discrepancy was noted between the size of the lesion that was first removed and the size predicted by imaging. Technically, MIS allows removal of multiple lesions through the same incision; however, since in case of multiglandular disease all parathyroid glands may be involved and identification by US is less successful due to the small average size of the enlarged glands [13], it is important that all glands be surgically inspected. Therefore we prefer to perform CNE in case enlargement of more than one gland has been diagnosed.

In three patients MIS was unsuccessful. One of these treatment failures was caused by an incorrect imaging diagnosis, in which an accessory thyroid gland was misinterpreted as being a parathyroid adenoma. In another case, there were two adenomas close to each other in the same anatomical location, and only the largest was visualized by preoperative imaging. However, in this case the MIS procedure was terminated after removal of the smaller one because no notice was made of the discrepancy between the size of the removed adenoma and that of the larger one visualized by US and found later at CNE. In the third case, the surgeon removed initially only a part of the predicted large adenoma and the remainder was left behind, which was later removed at CNE. These experiences emphasize the importance to correlate during MIS the size of the removed adenoma with the size predicted by imaging. Application of a test that allows rapid determination of the parathyroid hormone level in the blood at the end of the surgical procedure may also alert the surgeon to incomplete resection or the presence of a second adenoma in case the hormone level remains elevated. Such a test, which takes only 40 minutes to complete, was recently introduced at our institution as a routine procedure, allowing to perform re-operation within an hour in case of initial failure [23].

US showed an overall sensitivity in identifying parathyroid adenomas of 74% (solitary and multiple adenomas combined). Although we considered in our conservative approach all equivocal adenomas as 'negative' findings, these results are within the range (65%-85%) of those reported by others in identifying parathyroid adenomas with US imaging [13 15 18 20 24]. However, our positive predictive value of 98% in diagnosing parathyroid adenomas, and thus the nature of the lesions, by US was high compared to that of others (range 80%-97%) [13 15 18 20 24]. Because of the high accuracy in determining the nature of the lesions, we were also able to diagnose solitary parathyroid adenomas with high consistency (predictive value of 96%), something that is of crucial importance for successful MIS. In our study less then 10% of the patients had multiglandular disease, supporting the suggestion by some authors [25] that the true frequency of multiglandular involvement is lower than the 15% that is usually reported [3 4 5].

In our experience, characterizing the location of the solitary adenomas as 'superior', 'inferior' or 'aberrant' was very useful in the communication with the surgeon because it gave essential information about the anatomical localization of the lesion with its surrounding structures, needed for the implementation of the MIS procedure. Our approach to diagnosing a definite solitary adenoma was rather conservative to minimize the number of unsuccessful MIS procedures. Whether a definite adenoma was diagnosed or not, in all patients with the presentation of one or more equivocal lesions, primary CNE was performed. If we had considered the equivocal lesions to be all 'definite' adenomas or all 'negative', in both instances we would have been able to perform more successful MIS procedures; however, this would have been at the expense of substantially more surgical failures.

A limitation of our study is that the patient groups were taken as convenience samples (group I came before group II). As a result, temporal effects on the results cannot be excluded. For instance, in group II the clinicians could have been more familiar with the advantages of MIS compared to CNE. They may therefore have lowered their threshold by referring patients with minimal or no clinical symptoms of pHPT for group II of the study. Such patients are more likely to harbor relatively small adenomas which are more difficult to diagnose and operate upon. On the other hand, learning effects may have resulted in superior diagnostic and surgical performance in group II. As the magnitudes of these effects are unknown, comparison of the results of part I and part II of the study, should therefore be done cautiously. However, the goal of our study was not to compare the two patient groups but to determine the overall role of US as the primary imaging modality for identification and localization of parathyroid adenomas in patients with pHPT to undergo MIS.

In conclusion, MIS is an imaging-guided surgical technique for treatment of parathyroid adenomas that has considerable advantages compared to CNE. We have demonstrated that, using the criteria outlined above, US permitted successful selection of patients with pHPT for MIS in more than two thirds of the cases. The adjunctive diagnostic use of spiral CT scanning allowed the selection of only a few more patients for MIS and therefore, the added diagnostic value of CT may not have been worth the effort, cost and risk of a radiation hazard. However, in selected cases CT may play an important role in providing an operator-independent roadmap for the surgeon. Close cooperation between surgeon and radiologist is essential, because the MIS procedure can only be performed successfully when the surgeon is informed in detail about location and size of the adenoma that needs to be removed.

References

1 Clark OH, Duh QY. Primary hyperparathyroidism, a surgical perspective. Endocrinol Metab Clin North Am 1989; 268: 943-953

2 Heath H, Hobgson SF, Kennedy MA. Primary hyperparathyroidism: incidence, morbidity, and potential economic impact in a community. N Engl J Med 1980; 302: 189-193

3 Loevner LA. Imaging or parathyroid glands. Seminars in ultrasound, CT and MRI 1996; vol 17: 563-575

4 Higgins CB. Role of magnetic resonance imaging in hyperparathyroidism. Radiol Clin North Am 1993; 31: 1017-1028

5 Hopkins CR, Reading CC. Thyroid and parathyroid imaging. Seminars in ultrasound, CT, and MRI 1995; 16: 279-295

6 Van Heerden JA, Grant CS. Surgical treatment of primary hyperparathyroidism: an institutional perspective. Word J Surg 1991; 15: 188-192

7 Wheeler MH. Primary Hyperparathyroidism: a surgical perspective. Ann R Coll Surg Eng 1998; 80: 305-812

8 Salti GI, Fedorak I, Yashiro T et al. Continuing evolution in the operative management of primary hyperparathyroidism. Arch Surg 1992; 127: 831-837

9 Vroonhoven TJMV van, Dalen A van. Succesful minimally invasive surgery in primary hyperparathyroidism after combined preoperative ultrasound and computed tomography imaging. J Internal Medicine 1998; 243: 581-587

10 Smit PC, Borel Rinkes IHM, Dalen A van,Vroonhoven TJMV van. Direct minimally invasive adenectomy for primary hyperparathyroidism; an alternative for conventional neck exploration? Ann Surg 2000; 231: 559-565

11 Ghandur-Mnaymneh L, Cassady J, Hajianpour MA, et al. The parathyroid gland in health and disease. Am J Path 1986; 125: 292-299

12 Solbiati L, Pravettoni G, Ierace T. Collo in SIUMB (ed) Trattato Italiano di Ecografica 1993; 1: 80-115

13 Gooding GAW. Sonography of the thyroid and parathyroid. Radiol Clin North Am 1993; 31: 967-989

14 Randel SB, Gooding GAW, Clark HC, et al. Parathyroid variants: US evaluation. Radiology 1987; 165: 191-194

15 Reading CC, Charboneau JN, James EM, et al. High resolution parathyroid sonography. AJR 1982; 139: 539-546

16 Bonjer HJ, Bruining HA, Birkenhager JC, et al. Single and multigland disease in primary hyperparathroidism: clinically follow up, histopathplogy, and flow cytometric DNA analysis. World J Surg 1992; 16: 727-743

17 Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934; 26: 404-413

18 Stark DD, Gooding GAW, Moss AA. Parathyroid imaging: Comparison of high resolution CT and high resolution sonography. AJR 1983; 141: 633-638

19 NAS/NCR(1980). National Academy of Sciences/National Reasearch Council, Committee on the Biological Effects of Ionizing Radiations. The effects on Populations of Exposure to Low Levels of Ionising Radiation: 1980, BEIR III (National Academy Press, Washington)

20 Mazzeo S, Caramella D, Lencioni R et al. Comparison among sonography, double tracer subtraction scintigraphy, and double phase scintigraphy in the detection of parathyroid lesions. AJR 1996; 166: 1465-1470

21 Norman J, Chheda H. Minimally invasive parathyroidectomy facilitated by intraoperative nuclear mapping. Surgery 1997; 122; 998-1003

22 Costello DW, Norman J. Minimally invasive radioguided parathyroidectomy. Surg Onc Clin North Am 1999; 8: 555-564

23 Smit PC, Thijssen JHH, Borel Rinkes IHM, Van Vroonhoven TJMV. Peroperative PTH testing: confirmation of succesful surgical treatment of primary hyperparathyroidism. Ned Tijdsschr Geneesk 1999; 143: 742-46

24 Loyd MHN, Lees, WR, Milroy EJG. Pre-operative localisation in primary hyperparathyroidism. Clinical Radiology 1990, 41: 239-243

25 Ryan JAjr, Lee F. Effectiveness and Safety of 100 consecutive parathyroidectomies. Am J Surg 1997; 173: 441-444

Peroperative PTH testing:

confirmation of successful surgical treatment of primary hyperparathyroidism

7

Smit PC, Thijssen JHH, Borel Rinkes IHM, van Vroonhoven TJMV. Peroperative PTH testing: confirmation of successful surgical treatment of primary hyperparathyroidism. Nederlands Tijdschrift voor Geneeskunde 1999; 143 : 742 - 746

Summary

Objective To study the reliability and applicability of a rapid parathormone (PTH) test as predictor of successful surgical treatment of primary hyperparathyroidism.

Design Prospective.

Method All 35 consecutive patients undergoing surgery for primary hyperparathyroidism in the University Medical Center Utrecht, The Netherlands, between August 1997 and August 1998, were tested just prior to surgery, and immediately following adenomectomy. The rapid PTH test consisted of a modification of the computerized immunometric detection by chemoluminescence.
The decrease of serum PTH as estimated with the rapid test was correlated with surgical findings as well as postoperative serum calcium levels. In the first 25 patients (group A) the reliability of the test was investigated. In the next 10 patients (group B) the PTH test results were allowed to have implications for surgical management, i.e. an insufficient (<50%) decrease of serum PTH following adenomectomy resulted in immediate re-exploration.

Results The 35 patients, 22 women and 13 men, had a median age of 58 years (range: 22-80). The results obtained with our rapid PTH test correlated fully with both conventional PTH measurement techniques and postoperative serum calcium levels. In group A 21/25 patients showed adequate (>50%) decrease of their serum PTH levels; the 4 patients without such decrease were the ones displaying persistent postoperative hypercalcemia. In group B 9/10 patients had adequate PTH decrease immediately following adenomectomy, while in one patient this was only attained after further exploration and excision of a second adenoma. No false-positive or false-negative measurements were encountered.

Conclusion The rapid PTH-test used is a reliable predictor of successful adenomectomy for primary hyperparathyroidism, also in minimally invasive surgery.

Introduction

The purpose of the surgical treatment of primary hyperparathyroidism is to normalize the calcium concentration in the serum. It is therefore necessary during the operation to locate and remove the hyperfunctioning parathyroid tissue. In the majority of the cases there is one adenoma; but two, three, or even four adenomas occur in about 15% of the patients. Because the serum calcium concentration from a successful operation decreases very slowly, one normally must wait until the next postoperative day in order to be certain the intended normalization indeed has occurred. In those cases where the serum calcium concentration has not decreased, or decreased enough, a second operation must be performed under less favorable conditions for both the patient as well as the surgeon.

The parathyroid hormone (PTH) has a half-life of less that five minutes [1], and should in theory be able to be used to determine during the operation if all of the hyperfunctioning tissue is removed. Until recently, reliable measurement of the PTH concentration in the laboratory was too labor-intensive and too time-consuming for this purpose. Now faster methods for the measurement of the PTH concentration have become available, and the ideal of having proof during the operation will be successful, is clearly in sight.

The usefulness of a recently developed, rapid PTH measurement was tested and correlated for operative and postoperative findings in 35 patients who were operated for primary hyperparathyroidism. At the same time the effects of this new approach for the following surgical strategy was studied.

Methods

All consecutive patients between August 1997 and September 1998 (13 months) who were candidates for surgical treatment of their primary hyperparathyroidism were eligible for the study. The diagnosis 'primary hyperparathyroidism' was formed based on a repeated increased concentration of calcium and parathormone in the serum. At the same time, according to protocol, a localizing diagnostic was performed using Doppler ultrasonography and spiral computed tomography examination of the neck. The results of this determined if a conventional, systematic neck exploration was performed, than if a direct removal of the adenoma in a minimally invasive way was sufficient. This direct exploration has as its disadvantage that not all the parathyroid tissue is identified nor can it be macroscopically reviewed. For this limited procedure, just as with the conventional neck exploration, not identified diseased glands at imaging and exploration result in a persistent hypercalcemia.

At the beginning of the operation and eight minutes after the hyperfunctioning parathyroid tissue was removed, peripheral venous blood was drawn and a PTH measurement was done. In order to establish the reliability of the new measurement in the perioperative period, no surgical conclusions were drawn from the results of the PTH-values after resection in the first 25 patients (group A). In the following ten patients (group B) a decrease of PTH concentration of at least 50% was considered as evidence that all the hyperfunctioning tissue was removed. No decrease or a decrease of less than 50% was reason to immediately perform further neck exploration afterwards. If more adenomatous parathyroid tissue was found, a quick PTH-measurement was again done after its removal.

Measurement of parathormone

For the measuring of PTH a new modification of the automated immunometric (sandwich) measurement with chemoluminescence (Immulite, Diagnostic Products Corporation (DPC Holland), Apeldoorn) was utilized [2]. This measurement made use of two purified (cultured in goats) antibodies against, respectively, the first so-called N-terminal part (amino acids 1-34) and the last so-called C-terminal (amino acids 44-84) part of the PTH molecule. The C-terminal antibody is bound to a polystyrene bead and the N-terminal is recognized with the enzyme alkaline phosphatase, with which the chemiluminescence becomes activated after reaction with PTH. The measurement is directed towards the measuring of intact PTH; pieces of PTH show no cross-reaction in the assay.

The modification holds that a shorter incubation time is used than until now has been described: the original measurement has a reaction time of 60 minutes, while the modification is incubated for 30 minutes. The measurement is tolerant for serum as well as ethylene diamintetra-acetate (EDTA). In practice EDTA-plasma is worked with since the plasma and cells being separated from each other directly after the blood is drawn. After being received by the laboratory and centrifuged for four minutes, the assay is begun, which proceeds further automatically in the Immulite, which is made ready for the PTH-measurement in advance. After approximately 45 minutes the results are available after calculation with the attached microcomputer. The sensitivity of the shortened assay ($\sim$ 0.1 pmol/L), is practically identical to the original; the variation between measurements amounts to 5.3% at 4.8 pmol/L, 3.0% at 34.4 pmol/L, and 3.3% at 90 pmol/L (each time $n = 10$). The correlation between the long and the short method were determined in more than 100 samples; the correlation coefficient amounted to 0.992 at a gradient of 0.986, which says that the results were absolutely comparable.

Results

The study was performed with 35 patients with primary hyperparathyroidism. It involved 22 women and 13 men with a median age of 58 years (range: 22-80). The median serum concentrations of calcium and parathormone were, respectively, 2.75 mmol/L (ranges: 2.51-3.81; normal: 2.20-2.60), and 13.3 pmol/L (ranges: 2.3-148.0; normal for normocalcemia: <8 pmol/L). In 26 patients (group A, 19; group B, 7) a minimally invasive operation was performed. The other 9 patients (group A, 6; group B, 3) underwent a conventional neck exploration.

Group A (reliability of the assay)

Of the 25 patients from this group, 21 became normocalcemic after the operation (**Table 1**). The perioperatively measured decrease of the PTH serum concentration with these patients was, with a median decrease of 82%, unmistakable.
With the four patients who still showed hypercalcemia after the operation, the perioperatively measured PTH values showed no (two patients) or an insufficient decrease (15% and 30%). Of these four patients, two underwent in the meantime repeat surgery; at that a second parathyroid adenomas was found, after which this was removed and microscopically confirmed. Upon this the perioperative PTH concentration decreased significantly then and normocalcemia existed after the operation. The two other patients with persistent hypercalcemia are still waiting to be reoperated.

Group B (applicability of the assay)

This group consisted of 10 patients (**Table 2**). In 9 a significant decrease of the serum PTH concentration (median decrease: 87%) was determined during the operation. In one patient the PTH concentration barely decreased after resection of one adenoma (from 9.4 to 7.3 pmol/L). Further exploration followed immediately, by which a second adenoma was found and removed, followed with a significant decrease of the PTH concentration (from 7.3 to 1.2 pmol/L). All ten patients were normocalcemic after exploration.

In total was thus 33 times (30 times during primary exploration, 3 times during further exploration) perioperatively a significant decrease of the serum PTH concentration established and in all these 33 cases normocalcemia later existed, as proof of a successful exploration. In four cases (during the ‘reliability study’) the operation was ended, while no or only a limited decrease of the serum PTH concentrations was ascertained, which was followed by persistent hypercalcemia. There were in this patient group, therefore, no false-negative and no false-positive results found.

Table 1 Serum parathormone concentrations measured before and after resection of hyperfunctioning parathyroid tissue in 25 patients with primary hyperparathyroidism (Group A, reliability study).

	perioperative					postoperative
	serum PTH concentration in pmol/L			serum calcium concentration in mmol/L		normocalcemia
patient	preresection	postresection	decrease (%)	preresection	postresection	
1	14.0	1.4	90	2.75	2.27	yes
2	14.0	3.1	78	2.92	2.50	yes
3	8.5	0.9	89	2.66	2.18	yes
4	53.0	4.8	91	3.02	2.28	yes
5	11.4	0.1	99	2.68	1.97	yes
6	61.0	4.4	93	3.16	2.24	yes
7	12.3	2.3	81	2.75	2.11	yes
8	17.0	2.9	83	2.70	2.30	yes
9	12.0	1.0	92	2.59	1.94	yes
10	13.3	13.5	0	2.78	2.73	no *
11	27.3	2.4	91	3.01	2.18	yes
12	11.7	1.2	90	2.51	2.10	yes
13	21.0	14.2	33	2.81	2.71	no#
14	6.2	1.4	78	2.60	2.07	yes
15	25.8	1.9	93	2.87	2.35	yes
16	28.2	2.2	92	2.64	2.25	yes
17	13.9	11.9	14	2.79	2.71	no *
18	2.3	0.1	94	2.70	2.16	yes
19	11.3	0.9	92	2.63	2.25	yes
20	34.5	9.6	72	3.02	1.95	yes
10 b *	12.3	2.0	84	2.76	2.11	yes
21	4.1	2.0	52	2.70	2.20	yes
17 b *	11.5	1.3	89	2.72	2.39	yes
22	6.4	0.9	86	2.65	2.01	yes
23	15.0	4.2	72	2.94	2.40	yes
24	109.0	20.0	82	2.72	2.05	yes
25	4.6	4.5	0	2.90	2.65	no#

* reexploration is executed.

reexploration will be executed.

Table 2 Serum parathormone concentrations measured before and after resection of hyperfunctioning parathyroid tissue in 10 patients with primary hyperparathyroidism (Group B, reliability study).

	perioperative					postoperative
	serum PTH concentration in pmol/L			serum calcium concentration in mmol/L		normocalcemia
patient	preresection	postresection	decrease (%)	preresection	postresection	
1	8.3	1.5	82	2.75	1.94	yes
2	16.4	1.6	90	2.66	2.28	yes
3	8.7	1.4	84	2.60	2.14	yes
4	9.4	7.3 (1.2)	32 (84)	2.75	(2.13)	yes
5	148.0	11.3	92	2.90	1.95	yes
6	12.0	2.5	79	3.01	2.15	yes
7	10.0	3.9	61	2.80	2.10	yes
8	11.1	1.0	91	2.79	2.05	yes
9	35.1	4.7	87	2.90	2.10	yes
10	61.5	11.4	82	3.80	2.55	yes

Numbers between parentheses are values after reoperation and resection of a second adenoma.

Discussion

The results of our investigation showed that perioperative PTH-measurements can be of good use in determining the completeness of resection of hyperfunctioning parathyroid tissue and with that to predict the chance of success of the operative treatment of primary hyperparathyroidism.
This finding agrees with the recently published experiences of a group Swedish investigators [3]. Going by the definition that the PTH concentration should be decreased by at least 50% five minutes after resection and at least 60% 15 minutes after resection in order to be able to predict a positive result, they found a sensitivity of 86% by the 5 minute and 97% by the 15-minute definition. The specificity was 100%. The development of a rapid, but especially reliable PTH-assay brings a number of not to be undermined advantages with it. In the first place the patient can be placed in a prospect of greater certainty. Furthermore, a decrease in the number of non-successful explorations can be expected along with the accompanying complications of parathyroid surgery, which are seen mainly in repeat operations. The decrease of the necessity for repeat operations, and with it the decrease of supplementary examination and the number of hospital admittances will above all be cost-efficient. Finally, the development and applicability of the rapid PTH-assay can be seen as a definite step towards wide application of the direct, minimally invasive treatment of primary hyperparathyroidism.

Until now most experts saw as the golden standard the bilateral, systematic exploration of the neck in which all the four parathyroid glands are identified and inspected [4]. Not unjustly, incidentally, because with such a conventional neck exploration is the change of success in experienced hands high, 95 to 97%; that can not be said until now of less extensive explorations, of which the unilateral is the most applied. Now that a rapid PTH-assay is available to assure the success of the surgery, there is no hindrance standing in the way of ample application in the less invasive approach. One of those is the technique with which we, owing to the developments in radiology, such as echodoppler and spiral computed tomography examination, recently achieved very promising results [5]. It is then also to be expected that the indication for operative treatment of primary hyperparathyroidism will be more ample than suggested before [6].

Next to the rapid PTH-assay used by us are special ‘kits’ obtainable for some time which are so quick that the total time needed between collection of blood on the one side and the result of the PTH measurement on the other side amounts to only a quarter of an hour [7]. The high costs associated with this method however seem to matter when weighed against the time that is saved. It is true that we must wait 45 minutes for the results after collection of the blood samples using our method,

but the (expensive) procedure at the operation rooms do not have to be impeded by that. The practical solution that we found for that, and that is in the meantime being routinely applied with success, is the following;
The patient with primary hyperparathyroidism is one of the first to be operated in the daily schedule. When the surgeon feels that all the hyperfunctioning parathyroid tissue is removed, a blood sample is taken to check the PTH measurement and the operation is ended. After that the patient, such as usually is done, goes to the recovery room. There he/she stays in any case until the result of the PTH measurement is known. In the majority of cases (in this group 30 of the 35 patients) the PTH concentration provides immediately the assurance of a successful operation and the patient, as soon as it is anesthesiologically responsible, can be returned to the nursing ward. The patient, by whom an insufficient decrease was determined, went then from the recovery room back to the operation room, where the neck exploration was continued. The extra burden for the patient stays thus limited and our experiences teaches in the meantime that patients choose by far this design over the uncertainty that is characteristic to the conventional course of things.

In summary, it seems from this study with a rapid perioperative PTH assay that this method can reliable predict the result of the operation and that it must be possible, by a consistent application to reduce the number of unsuccessful explorations for primary hyperparathyroidism to practically none, even when less invasive approaches become applied.

References

1 Davies C, Demeure MJ, St. John A, Edis AJ. Study of intact (I-8) parathyroid hormone secretion in patients undergoing parathyroidectomy. World J Surg 1990; 14: 355-360

2 Michelangeli VP, Heyma P, Colman PG, Ebeling PR. Evaluation of a new, rapid and automated immunochemiluminometric assay for the measurement of serum intact parathyroid hormone. Ann Clin Biochem 1997; 34: 97-103

3 Bergenfelz A, Isaksson A, Linddblom P, Westerdahl J, Tibblin S. Measurement of parathyroid hormone in patients with primary hyperparathyroidism undergoing first and reoperative surgery. Br J Surg 1998; 85: 1129-1132

4 Van Heerden JA, Grant CS. Surgical treatment of hyperparathyroidism: an institutional perspective. World J Surg 1991; 15: 688-692

5 Van Vroonhoven TJMV, van Dalen A. Successful minimally invasive surgery in primary hyperparathyroidism after combined preoperative ultrasound and computed tomography imaging. J Intern Med 1998; 243: 581-587

6 Smit PC, van Dalen A, van Vroonhoven TJMV. Strategy in asymptomatic and mildly symptomatic primary hyperparathyroidism, new arguments for the surgical option. Neth J Med 1998; 52: 95-99

7 Irvin GL III, Deriso GT III. A new, practical intraoperative parathyroid hormone assay. Am J Surg 1994; 168: 466-468

Perioperative parathormone assessment during surgery for primary hyperparathyroidism;

Comparison of four techniques

8

Submitted for publication as Smit PC, Borel Rinkes IHM, van Zon JPHM, van Vroonhoven TJMV, Thijssen JHH. Perioperative parathormone assessment during surgery for primary hyperparathyroidism; Comparison of four techniques

Abstract

Objective To test four different non-portable PTH assays (Immulite Regular assay, Immulite Turbo assay, Advantage Regular assay and Advantage Turbo assay) as alternative for (expensive) portable PTH assays in predicting surgical outcome in primary hyperparathyroidism.

Methods All consecutive patients with biochemically proven primary hyperparathyroidism were enrolled in this study. A decline of >50% in PTH concentration (in a sample taken 8 minutes after resection) was defined to be predictive of postoperative normocalcemia, a drop of less than 50% to indicate persistent disease. The Immulite Regular assay was considered the reference test for perioperative measurement. We prospectively tested 192 samples from 90 patients by the Immulite Regular and Immulite Turbo assay. In addition, 101 samples from 53 patients were tested with the Advantage Regular and Advantage Turbo assay.

Results In 80 patients postoperatively normocalcemia was correctly predicted after a median drop in PTH concentration of 84.9% (all over 50%, measured with Immulite Regular). When comparing preoperative and postoperative PTH levels, the median decline using the Immulite Turbo assay was 84.0%, in the Advantage Regular assay was calculated to be 78.2% versus 76.1% in Advantage Turbo assay. Comparative analysis of Immulite Regular and Immulite Turbo assays showed that they correlated extremely well ($r=0.987$), as for Advantage Regular and Advantage Turbo ($r=0.993$). Results of Immulite Regular and Immulite Turbo assays versus Advantage Regular and Advantage Turbo assays were discordant in three patients (all of whom were normocalcemic on the first postoperative day).

Conclusion Both the Immulite Regular and Immulite Turbo assays were found to be highly accurate and moderately superior to the Advantage Regular and Advantage Turbo assays when drawn at 8 minutes with a 50% guideline. All four alternatives were much less expensive than the portable kits.

Introduction

The goal of surgical treatment in primary hyperparathyroidism (pHPT) is normalization of serum calcium. Since this takes at least 24 hours both surgeon and patient are uncertain about the effect of the exploration until the first postoperative day. With the development of less invasive techniques as alternatives for conventional neck exploration (CNE) in the treatment of pHPT, the need for perioperative assurance about the effect of the exploration has increased. The short half-life (< 3 minutes) of intact parathormone (1-84) (PTH), combined with suppression of PTH secretion for hours after parathyroid adenomectomy, contribute to fast clearance from the circulation. Early studies on intraoperative PTH testing to ascertain the success of unilateral explorations, by Nussbaum [1] and Irvin [2] reported the results of modified immunoradiometric assays (IRMA). Although this test provided results within 25 minutes, it has not been widely accepted. The short half-life of isotopes (and the 'shelf-life' of these intraoperative PTH assays), the necessary safety precautions (including proper disposal of waste products), a false negative rate of 15%, and the associated high costs, initially limited use of the assay to a few specialized centers [2]. Other rapid tests were developed but despite the technological advances of these tests the potential of intraoperative measurement was not realized until the introduction of modified immunochemoluminometric assay kits that can be used in the operating theatre [3 4]. Nowadays, these commercially available portable kits can perform PTH measurements within 15 minutes with sensitivity rates up to 96%, specificity of ~100% and an overall accuracy of 97% [3 5]. It cannot be denied that these tests are highly effective in providing true intraoperative results, but the need for instrument performance checks, for generating calibration curves and for assay quality control before surgery and the high cost preclude their widespread use. In the search for an alternative rapid PTH assay to these portable kits, we have evaluated the accuracy of four non-portable 'quick' tests as predictors of surgical success in primary hyperparathyroidism. The following assays were investigated: 1) the Immulite Regular PTH assay (60-minute incubation), 2) the Immulite Turbo PTH assay (10-minute incubation), 3) the Advantage Regular PTH assay (25-minute incubation), and 4) the Advantage Turbo PTH assay (12-minute incubation).

Methods

Parathormone assays

Parathormone levels in blood were assessed by four different commercially available, non-portable PTH assays. Two manufactured by Diagnostic Products Corporation (DPC, Los Angeles, Ca, USA) and two manufactured by Nichols Institute Diagnostics (San Juan Capistrano, Ca, USA). Both of these companies market a Standard assay (DPC: Immulite Regular assay and Nichols: Advantage Regular), and a more rapid, so-called Turbo assay (DPC: Immulite Turbo assay and Nichols: Advantage Turbo assay).

I) The Immulite Regular and the Immulite Turbo assays are analyzed using the DPC Analyzer. Both assays use a pair of antibodies, respectively directed at the C-terminal part of PTH (immobilized to solid phase) and the N-terminal region. The main difference between these assays is the much shorter time of incubation when the Turbo-mode is utilized, requiring a separate set of reagents. The Immulite Turbo assay can only be utilized in the Turbo-mode of the Immulite software. This results in a less sensitive assay, the Immulite Regular assay having a lower limit of detection for PTH of 0.4 pmol/L whereas the sensitivity of the Turbo equals 1 pmol/L. Interassay variations for both tests during the year 2000 were between 7 and 10%.

After proper calibration of the Analyzer, total time between start of processing an EDTA-plasma sample and the first result is 75 minutes for the Immulite Regular assay and 15 minutes for the Immulite Turbo assay. In the Regular mode 50 µl and in the Turbo mode 100 µl of EDTA-plasma is used.

II) The Advantage Regular Intact PTH and the Advantage Turbo Intact PTH assays, of Nichols Institute Diagnostics. In both variants of these assays identical reagents are used, the only difference in processing is the incubation time and the requirement for special software to operate the Analyzer in the Turbo-mode. The sensitivity of the Advantage Regular assay is 0.5 pmol/L whereas no official data are available for the Advantage Turbo assay but its sensitivity is about 1 pmol/L. Interassay variation measured over the past year of the Advantage Regular assay was approximately 11%, whereas no such data are available for the Advantage Turbo assay.

After proper calibration of the Analyzer, total time between start of processing an EDTA-plasma sample and the first result is approximately 40 minutes in the Advantage mode and 17 minutes in the Turbo mode. Both the Advantage Regular assay and the Advantage Turbo assay use 150 µl of EDTA-plasma.

Patients

All consecutive patients with biochemically proven primary hyperparathyroidism were enrolled in this prospective study after informed consent was obtained. Previous (para)thyroid surgery was considered a criterion for exclusion. In an earlier study we had tested the reliability and applicability (reliability study) of the Immulite Regular assay in 25 patients. A decline of more than 50% in PTH concentration (in a sample taken 8 minutes after resection) was defined to be predictive of postoperative normocalcemia, a drop of less than 50% to indicate persistent disease. Once the Immulite Regular test results were proven to correlate fully with postoperative serum calcium levels, we introduced it to our surgical management protocol [6].

Study design

In the present study the Immulite Regular assay was considered the reference test for perioperative PTH measurement. We prospectively tested 192 samples from 90 patients by the Immulite Regular assay. Once the Immulite Turbo assay became available we tested the same 192 samples with that as well, and compared the results of both methods. In addition, 101 samples from 53 patients were tested with the Advantage Regular assay and the Advantage Turbo assay. Results of these two tests were correlated to postoperative calcium levels as well as to the Immulite Regular assay. In addition, we compared the results of the Advantage Turbo and the Advantage Regular assays.

Protocol

One day prior to surgery the Endocrine laboratories were informed about the scheduled exploration so that such necessary preparations as calibration of the Analyzer could take place. Baseline peripheral plasma samples (3 ml EDTA (k3) Vacutainer®) were taken at the operation room after anesthesia was induced but before exploration. Eight minutes after resection of a suspected adenoma the next sample was taken, transported to the Endocrinology laboratories and subsequently analyzed. After exploration, patients were extubated in the operation room and transported to the recovery unit. Patients were only sent back to the surgical ward if the test results were indicative of successful exploration. If not, they were taken back to theatre, as soon as it was ready, for re-exploration.

Operative success was defined as normalized serum calcium levels on the first postoperative day and 1 week and 1 month later.

Depending on the preoperative imaging results patients underwent either minimally invasive adenomectomy (MIA) or conventional neck exploration (CNE). If a solitary adenoma was visualized, a local procedure through a 2-3 cm incision at the ventral border of the sternocleidomastoid muscle was performed as described elsewhere [7]. After identification and resection of the adenoma the procedure was terminated. If no adenoma was found, however, the exploration was converted into CNE, comprising a systematic, bilateral exploration through a 10-12 cm collar incision, with identification of the four parathyroids and resection of the causative adenoma(s) based on gross morphologic features. If MIA (or CNE) failed the reexploration consisted of a CNE.

Results

Ninety patients with a biochemically proven pHPT were selected for surgery. Their median age was 59 years (range 22-81), with women outnumbering men 62 to 28. The median preoperative calcium level was 2.89 mmol/L (2.55-4.10; normal 2.20-2.60) while the PTH level was 14.1 pmol/L (range: 10-220; normal <8 pmol/L). Based upon preoperative imaging results 64 patients were selected for MIA, 26 for CNE. Two samples (one baseline sample and one postresection sample, total 156 samples) were drawn from 78 patients, three (total 36 samples) from the other 12, in whom multiple gland disease was suspected or to ascertain success after delayed fall in PTH.

In 80 patients postoperative normocalcemia was correctly predicted after a median drop in PTH concentration of 84.9% (all >50 %, measured with Immulite Regular assay). After a thorough exploration (CNE) one patient displayed a drop in PTH concentration of 47.4% at 8 minutes after resection. However, as an exception to the protocol, this patient did not undergo immediate re-exploration because during exploration all parathyroid tissue had been identified (one adenoma and three normal parathyroid glands). The chance of a fifth parathyroid gland was considered, but rejected because of the very low incidence of supernumerary glands. The next day the patient's serum calcium level was normal (2.25 mmol/L).
In two patients falls of 40% and 48%, respectively, suggested surgical failure. Because this decline was so close to the 50% cut-off point we decided to draw a third sample at 30 minutes after resection. These samples showed respective declines of 94% and 99.5% and next day their calcium levels were normal, and this was confirmed during follow-up. Seven patients showed a fall in PTH of less than 50% (falls of 25%, 12%, 2%, increases to 123%, 124%, 140% and 152%). All were re-explored (as is discussed below) and a (second) causative adenoma was found and resected, after which their serum calcium concentrations fell to normal.

Sixty-four patients underwent MIA. Fifty-nine (92%) showed an adequate decline in PTH level and were normocalcemic in the postoperative period. Minimally invasive adenomectomy was followed by an inadequate fall in PTH, requiring immediate re-exploration in two patients at which a 'missed' causative adenoma was found and resected. Both became normocalcemic postoperatively. The other three displayed persistent abnormality and were re-explored at a later stage (these failures were monitored during the 'reliability study'). At re-exploration a (second) adenoma was resected in all of them (multiple gland disease in two, missed adenoma in one) and their serum calcium reverted to normal.

After CNE, 24/26 patients (92%) showed a fall in PTH concentration of more than 50 %, and all were proven to be normocalcemic. The other two patients had persistent disease after a fall of less than 50%, necessitating re-exploration. In the first patient a second adenoma was found in the thymus, while an additional adenoma was localized and subsequently resected from the mediastinum in the second. Both became normocalcemic after re-exploration.

Comparative analyses of PTH assays

Comparative analysis of the results of Immulite Regular and Immulite Turbo assays (192 samples) yielded the following equation:
Immulite Turbo = 0.807 x Immulite Regular + 1.2; $r = 0.987$ ($p < 0.0001$) (**Figure 1**).
This means that both methods correlated extremely well ($r = 0.987$), though the test results with the Immulite Turbo assay are somewhat lower (Immulite Turbo = 0.807 x Immulite Regular) than those with the Immulite Regular assay.
Comparing baseline values and postresection values measured by the Advantage Regular and Immulite Regular assays, gave the following equation:
For baseline Advantage Regular = 0.701 x Immulite Regular + 1.0; $r = 0.966$ and for postresection Advantage Regular = 0.917x Immulite Regular + 0.5; $r = 0.930$ (**Figure 2**). This implies that the baseline values are 1.4 times higher when measured with Immulite Regular assay, while postresection values are almost equal. As a result the decline in PTH levels is relatively smaller in the Advantage Regular assay.

The results of 101 samples from 53 patients tested with Advantage Regular assay and Advantage Turbo assay showed:
Advantage Turbo = 1.07x Advantage Regular - 0.5; $r = 0.993$ (**Figure 3**), meaning that these two techniques also correlate extremely well.

Figure 1 Comparative analysis of Immulite Regular assay and Immulite Turbo assay.

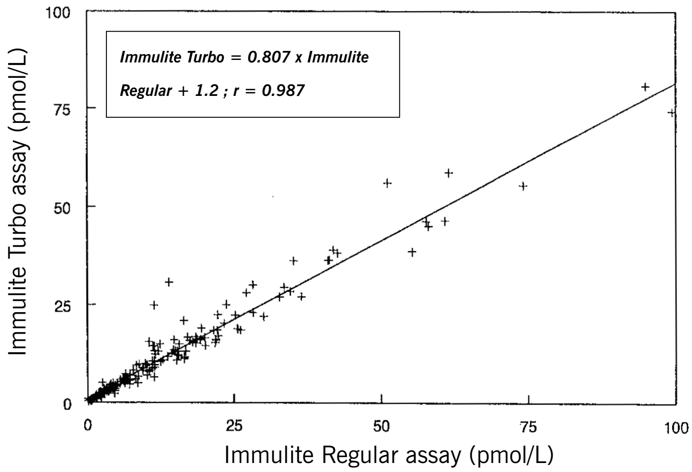


Figure 2 Comparative analysis of Immulite Regular assay and Advantage Regular assay.

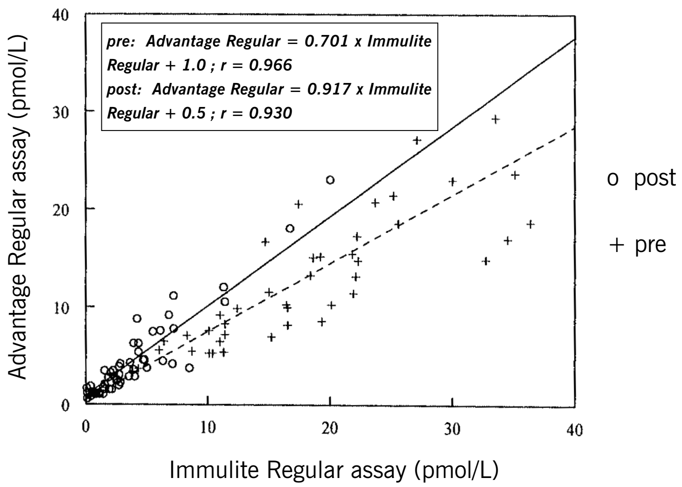
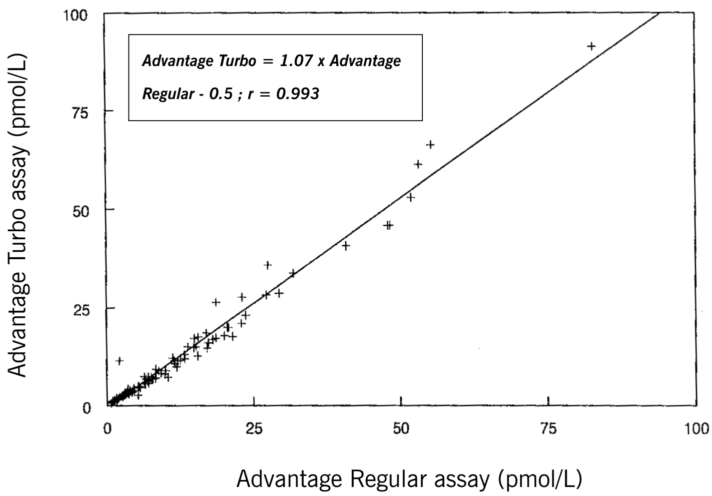


Figure 3 Comparative analysis of Advantage Regular assay and Advantage Turbo assay.



In calculating costs (for all four techniques) the following factors were considered: materials (reagents) used, personal salaries and wages, and overhead costs. We calculated the costs per patient (two assays) to be approximately 100 US dollars.

Discrepancies in parathormone assays

When comparing preoperative and postoperative PTH levels, the median decline using the Immulite Regular assay was 84.9% (range -99.6 to +153.8). Similarly the median decline as judged by the Immulite Turbo assay was 84.0% (- 97 to +153). The only discrepancy between these two methods was a patient in whom the Immulite Regular assay showed a drop of 57.3%, while the Immulite Turbo assay showed a drop of only 48.5%. The postoperative serum calcium, however, returned to normal on day one.

The median decline in the Advantage Regular assay was calculated to be 78.2% (-92.7 to +125.7) versus 76.1% in Advantage Turbo (-90.6 to +121.6).
The results of the Immulite Regular and Immulite Turbo assays versus the Advantage Regular and Advantage Turbo assays were discordant in three patients (all of whom were normocalcemic on the first postoperative day). In the first patient, the Immulite Regular and Immulite Turbo assays showed declines of 90% and 79%, respectively, while the Advantage Regular and Advantage Turbo assays recorded declines of 44% and 41%. In the second patient declines of 72% and

65% were observed in the Immulite Regular and Immulite Turbo assays. In contrast, rises to 126% and 122% of baseline values were observed using the Advantage Regular and Advantage Turbo assays. The adenoma in this patient, however, was very large and was accidentally fragmented during resection.
In the third patient a delayed fall in PTH was seen: a decrease of 52% was observed with the Immulite Regular and Immulite Turbo assays, but a fall of 9% and a rise of 20% were found by the Advantage Regular and Advantage Turbo assays respectively. However, PTH concentration measured in the 30 minute sample showed concentrations of 5.6% and 9.5% compared with baseline values using Advantage Regular and Advantage Turbo assays.

Discussion

Rapid PTH assay has become essential with the introduction of limited forms of parathyroid surgery. The use of portable non-radioactive kits that can be carried on a trolley has allowed assays to be performed in the operating theatre providing true intraoperative information. As a result, operating time and hospital stay can be reduced, leading to cost savings. Chen et al [8] reported a 50% reduction in hospital charges with outpatient minimally invasive parathyroidectomy. Although the reliability of the portable tests they used was reported to be excellent, the costs (approximately 1,000 US dollar a test) were about one third of mean total hospital charges per patient (3,174 US dollars). In our experience the mean total costs for MIA were calculated to be approximately 1,200 US dollars [9], which included the costs for the Immulite Regular assay (approximately 100 US dollars a test). Although the advantages of a portable kit, i.e. true intraoperative information on surgical outcome, precluding the need for second procedures, are evident, the high costs of such kits outweighs their advantages. The Immulite Regular test gave results within 75 minutes. It correlated in 97% of patients (all but one) with the postoperative serum calcium, and was concluded to be very reliable.

Despite the success of the perioperative PTH assays the following limitation should be noted. In three patients postexcision values fell to near 50% of the preoperative figure. The surgeon judged these patients to be cured and they were not immediately re-explored. This was confirmed in two patients after that a second postexcision sample showed an adequate decline. The cause of delayed fall in PTH concentration was not clear, but a low initial baseline PTH concentration and the manipulation of the adenoma during mobilization are possible reasons [10]. Manipulation of an adenoma may result in release of PTH or of proteins that resemble PTH that can potentially interfere with the assay. In addition, the use of a

50% decline after 8 minutes as a cut-off level does not take in account inter-individual variability in PTH half-life [10 11].

The Immulite Turbo assay was concluded to be a reliable test, which correlated extremely well with the Immulite Regular assay. Only in one patient was a fall of 57.3% shown by the Immulite Regular assay and close to 50% by the Immulite Turbo assay. No other problems were encountered, and it produced results within 15 minutes. Taking into account this and other examples of 'delayed' decline in PTH levels following correct surgery, we believe it is advisable that, in cases of PTH falls close to 50%, to preclude the possibility of a delayed fall, a third sample should be taken before deciding on re-exploration.

From a logistic point of view the procedure might be as follows: 8 minutes after resection the sample will be drawn; delivery to the Endocrine laboratory takes a little under 10 minutes. Since the Analyzer has been calibrated in advance, processing can take place immediately, providing results within 15 minutes. In total, test results become available after approximately 30 minutes. The surgeon can thus await the results with the patient under anesthesia, so avoiding the need for later re-intubation and re-exploration when the initial operation was not successful.

The Advantage Regular and Advantage Turbo assays were concluded to be less accurate than the Immulite Regular and Immulite Turbo assays, though the reasons for this remain unclear. However, we may speculate that differences in standardization of instruments and/or the detection of additional fragments of PTH by the latter two tests might explain the difference. The discrepancies between the methods do not necessarily prevent the use of the Advantage Regular and Advantage Turbo assays as perioperative or intraoperative PTH assays. Using a guideline of 50% decline at 8 minutes produces suboptimal results in both assays, and the test should therefore be prolonged when using Advantage Regular and Advantage Turbo assays.

In conclusion, the use of a perioperative PTH assay is essential in the treatment of primary hyperparathyroidism. Both the Immulite Regular and Immulite Turbo assays were found to be highly accurate and moderately superior to the Advantage Regular and Advantage Turbo assays when drawn at 8 minutes with a 50% guideline. All four alternatives were much less expensive than the portable kits.

References

1 Nussbaum SR, Thompson AR, Hutcheson KA, et al. Intraoperative measurement of parathyroid hormone in the surgical management of hyperparathyroidism. Surgery 1988; 104: 1121-1127

2 Bergenfelz A, Isaksson A, Lindblom P, Westerdahl J, Tibblin S. Measurement of parathyroid hormone in patients with primary hyperparathyroidism undergoing first and reoperative surgery. Br J Surg 1998; 85: 1129-1132

3 Irvin III GL, Deriso III GT. A new, practical intraoperative parathyroid hormone assay. Am J Surg 1994; 168: 466-468

4 Kao PC, van Heerden JA, Taylor RL. Intraoperative monitoring of parathyroid procedures by a 15-minute parathyroid hormone immunocheminoluminometric assay. Mayo Clin Proc 1994; 69: 532-537

5 Boggs JE, Irvin GL III, Molinari AS, Deriso GT. Intraoperative parathormone monitoring as an adjunct to parathyroidectomy. Surgery 1996; 120: 954-958

6 Smit PC, Thijssen JHH, Borel Rinkes IHM, van Vroonhoven TJMV. Peroperative PTH testing: confirmation of successful surgical treatment of primary hyperparathyroidism. Ned Tijdschr Geneesk 1999; 143: 742-746

7 Smit PC, Borel Rinkes IHM, van Dalen A, van Vroonhoven TJMV. Direct, minimally invasive adenomectomy for primary hyperparathyroidism; an alternative to conventional neck exploration ? Ann Surg 2000; 231: 559-565

8 Chen H, Sokoll LJ, Udelsman R. Outpatient minimally invasive parathyroidectomy: a combination of sestamibi-spect localization, cervical block anesthesia, and intraoperative parathyroid hormone assay. Surgery 1999; 126: 1016-1022

9 Smit PC, Liem MSL, Borel Rinkes IHM, van Vroonhoven TJMV. Cost-analysis of minimally invasive surgery and conventional neck exploration for primary hyperparathyroidism. Submitted.

10 Sokoll LJ, Drew H, Udelsman R. Intraoperative parathyroid hormone analysis: a study of 200 consecutive cases. Clin Chem 2000; 46: 1662-1668

11 Libutti SK, Alexander HR, Barlett DL, et al. Kinetic analysis of the rapid intraoperative parathormone assay in patients during operation for hyperparathyroidism. Surgery 1999; 126: 1145-1151

12 Tommasi M, Broncchi A, Benucci A, et al. Intraoperative fall in plasma levels of intact parathyroid hormone in patients undergoing parathyroid adenomectomy. Int J Biol Markers 1995; 100: 206-21

Cost-analysis of minimally invasive surgery and conventional neck exploration for primary hyperparathyroidism

9

Submitted for publication as Smit PC, Liem MSL, Borel Rinkes IHM, van Vroonhoven TJMV. Cost-analysis of minimally invasive surgery and conventional neck exploration for primary hyperparathyroidism.

Abstract

Objective To obtain knowledge on cost-relations between minimally invasive adenomectomy and conventional neck exploration in patients with primary hyperparathyroidism.

Summary background data Imaging modalities and measurement of perioperative parathormone concentration facilitate successful minimally invasive adenomectomy. As a result reduction in operative time and admission days may be anticipated together with potential reduction in costs.

Methods Prospectively, 164 consecutive patients with biochemically proven primary hyperparathyroidism were enrolled. Because of variation in imaging protocol over time, 126 patients underwent ultrasonography and computed tomography; in 38 patients ultrasonography was the sole modality. Data were collected from the first preoperative surgical consultation to discharge from follow-up. Costs were calculated by multiplying patients' resources by unit costs. To obtain insight in the effect of changing appreciable variables multiple sensitivity analyses were performed.

Overall 123 patients were selected for minimally invasive adenomectomy, 41 for conventional neck exploration. Mean costs for minimally invasive adenomectomy were calculated to be € 1288 +/- 431 (mean, +/- SD) and for conventional neck exploration € 2106 +/- 1070. Sensitivity analyses showed that an increase in total average costs of 63%, an increase in operative time to 272 minutes, prolongation of admission with 2.5 days, or a failure rate of 54% in the minimally invasive adenomectomy group would result in a break-even point with equal costs of both alternatives.

Conclusion Minimally invasive adenomectomy, including preoperative imaging is less expensive than conventional neck exploration in the treatment of primary hyperparathyroidism.

Introduction

For many years conventional neck exploration (CNE) has been the gold standard in the surgical treatment of primary hyperparathyroidism (pHPT), but with the advent of minimally invasive surgery, this pre-eminence has been questioned. As primary hyperparathyroidism is caused by a solitary adenoma in the vast majority of cases, CNE involves unnecessarily extensive exploration of normal parathyroid glands and prolonged operating time. Several authors have recommended unilateral neck exploration for that reason [1 2], and moreover, direct adenomectomy can now be performed with promising results [3 4 5].

Recently, we have introduced a technique of direct, minimally invasive adenomectomy (MIA) based on preoperative localization studies by ultrasonography (US) and spiral computed tomography scanning (CT) [6].

The results of this approach in our first 110 patients led us to conclude that MIA is a safe and effective alternative to CNE and may replace CNE in approximately two thirds of patients with pHPT [7].

Given current limited resources, it is of vital importance to obtain knowledge on cost-relations between these two alternatives. The current study contains a prospective cost-analysis of 164 consecutive patients undergoing CNE or MIA for primary hyperparathyroidism. In addition, we have performed sensitivity analyses to obtain an impression of the effect of changes in particular variables, for example operative time and admission time.

Methods

Patients

Between October 1994 and July 2000, 164 patients with biochemically proven primary hyperparathyroidism were enrolled in this study. Previous (para)thyroid surgery, familial hyperparathyroidism and multiple endocrine neoplasia syndrome were considered criteria for exclusion. After informed consent had been obtained for MIA, when this was thought to be possible, the patient was scheduled for preoperative imaging using US and CT. If the test results unequivocally indicated solitary disease the patient was advised to undergo MIA. On the other hand, if test results were equivocal or indicated multiglandular disease the patient was advised to undergo CNE. Surgery took place during a regular hospital admission and patients were discharged after surgery when they were able to look after themselves unaided and only needed oral analgesics for pain management.

Protocol

In this study four sub-groups are identified on basis of a) variation of preoperative imaging protocols over time b) the introduction of a perioperative parathormone (PTH) assay in late 1998. In the first series of 65 patients (October 1994 - March 1997) both US and CT were performed as preoperative localization studies. In the second series (April 1997 - October 1998, 45 patients) US was used alone unless its results were inconclusive, when CT was added. Because initial imaging with US produced inferior results [7] we reintroduced both modalities in the routine as preoperative work-up since then (November 1998 - July 2000, 54 patients). As we have described elsewhere, we started in June 1998 to use a perioperative PTH assay to predict the success of surgery for primary hyperparathyroidism, after the assay had been shown to agree fully with both conventional PTH assays and postoperative serum calcium measurements in over 100 patients [8].

Data collection

For the purpose of this cost analysis resources of 164 patients were prospectively measured. Resources before inclusion were not included as these were considered to be equal for all patients with primary hyperparathyroidism (i.e. diagnostic procedures for the diagnosis of primary hyperparathyroidism).

Data were collected from the first (preoperative) surgical consultation at the outpatient department to discharge from follow-up and counted for all 164 patients.

It was expected that all patients would receive regular intravenous anesthesia and be monitored on a normal ward postoperatively. Nevertheless, we recorded type of anesthesia and level of care (i.e. intensive care, medium care or normal care).

Procedures and measurement of resources

As the result of both operations is the same, we chose to perform a cost-minimisation-analysis [9]. A hospital-perspective was taken, since it is unlikely to expect differences in societal costs. The following parameters were identified as appreciable units and counted for each patient;

Before admission:

1 preoperative consultation (including laboratory testing)

2 imaging strategy (ultrasonography, computed tomography, nuclear mapping)

Admission:

3 total time in operating theatre (minutes), operation time (minutes) defined as the time between skin incision and - closure, time on recovery ward (minutes)

4 number of days in hospital

5 perioperative parathormone assay

6 in-hospital complications: conversion in CNE, reexploration, and miscella-

neous costs due to failed surgery, bleeding or infection, vocal cord paralysis, clinical hypocalcemia
7 laboratory tests

After discharge
8 number of postoperative consultations (outpatient department, emergency room)
9 late post-operative complications (described under 6)
10 miscellaneous costs due to recurrent disease (list 1-10)

Calculation of costs

Costs were calculated by multiplying patients' resources by unit costs [10]. The costs of materials and anesthesia, considered equal in both groups and based on average consumption, were provided by the department of financial administration of the University Medical Center Utrecht (The Netherlands), based upon 1999 guidelines.
Costs for nursing and medical personnel were calculated using the bottom-up principle [11]. According to this principle costs are calculated based on actual consumed time and resources. Based on personnel salaries and wages (1999 guideline) costs were calculated per time unit (minute) and multiplied by actual consumed time during operation and recovery time.
Costs for hospital days and outpatient consultations were calculated according to the guidelines of the Dutch Ministry of Health, Welfare and Sports issued in 1999 [12] and include all relevant overhead costs of administration and management, other hospital departments (cleaning, maintenance) and housing. General overhead costs were not used, since these figures are inaccurate and not generally representative on account of inter-hospital variability in financial systems. Costs of PTH assays and other laboratory tests were provided by laboratory administration of the University Medical Center Utrecht (The Netherlands). In cases of clinical hypocalcemia patients were treated with oral calcium (CalciumSandoz®) and alfacalcidol (Etalpha tablets®). Average retail prices for medication in the Netherlands were used [13].
All costs were calculated in Euro's (€). The official exchange rate at January 15, 2001 was 1€ = 0,9439 US Dollar.

Outcome assessment

The clinically most relevant outcome of surgical intervention in pHPT is failure or success, defined respectively as postoperative serum calcium concentrations above or below 2.60 mmol/L.

Sensitivity analysis

Sensitivity analyses give insight into the effects of change of an important variable on total average costs. Variables were identified to be important if their costs were appreciable in relation to the total costs and if they were liable to significant change (for example operative time or admission time). We chose to perform a so-called threshold analysis of each variable. This analysis uses the basic assumption that total average costs are equal in both alternatives. Then, the percentage in change of the variable is calculated. This gives insight into the degree of change, which is required to eliminate differences in costs.

The following four variables were identified:

1 Operating time. Individual variation in personal skills and experience influences operating time.
2 Admission days. Duration of admission varies between different reported studies. We calculated (a) how long an MIA patient's admission could be prolonged to bring the costs up to those of CNE and (b) the effect on CNE costs of reducing admission to one day.
3 Failure rate. Failure rate varies in MIA and CNE with individual experience.
4 Imaging. Conventional exploration can be done safely and effectively without preoperative imaging. For comparative purposes we therefore also calculated total average costs in MIA with all imaging costs charged to MIA.

Finally, we performed a fifth sensitivity analysis based upon the assumption that PTH assay can be performed in all future patients with primary hyperparathyroidism. Consequently, surgical failure will be identified within one hour after surgery and this will result in immediate re-exploration without the additional costs of secondary admission, imaging and laboratory tests. We calculated the costs of MIA and CNE if PTH assay was performed in all cases.

Statistical analysis

Costs are presented as means with their standard deviation. For normally distributed, continuous data the Student's t-test was used to detect statistically significant differences between groups. Not normally distributed data were represented as medians with their interquartile ranges (IQR). We used the Mann-Whitney U-test to test differences between medians. A chi-square statistic was used to test independence between two categories of data. If an expected value of one of the categories was less than five, we used a Fisher-exact test. A p value of <0.05 was considered statistically significant.

Results

Patients

Resources were recorded for 123 patients in the MIA group, 41 in the CNE group. Patients' characteristics are listed in **Table 1**. All patients underwent US, and 126 patients additionally CT. Two patients underwent (on their own request) additional sestamibi-technetium99m scintigraphy (Sestamibi scintigraphy) after inconclusive US and CT to exclude the possibility of mediastinal adenoma. All patients were treated in normal hospital setting. No differences were recorded in the type of anesthesia and intensity of care.

Minimally invasive adenomectomy group (123);
Minimally invasive adenomectomy was immediately successful in 113 patients (92%), as judged by postoperative normocalcemia, recorded on the first postoperative day. Because the localized adenoma could not be found during initial exploration, MIA was converted to CNE in four patients resulting in postoperative normocalcemia. In the period before the implementation of PTH assay to our protocol, three patients displayed persistent hypercalcemia in the postoperative period and underwent successful reexploration at a later stage. Perioperative PTH assay identified three 'potential failures' after which immediate re-exploration followed, which resulted in resection of the causative adenoma.
Initial success, defined as postoperative normocalcemia at the first postoperative day was thus recorded in 120 patients (98%) (113 immediate successes + 4 converted MIA + 3 immediate re-explorations).

Conventional Neck Exploration group (44);
Two (5%) failures were recorded after conventional exploration. The first patient displayed persistent hypercalcemia on the first postoperative day and was re-explored at a later stage, during which a third, initially missed adenoma was found in the retrosternal thymus. Perioperative PTH assay correctly predicted persistent hypercalcemia in the second patient after three normal parathyroid glands were identified but no adenoma could be localized in the neck. Additional Sestamibi scintigraphy localized the missing adenoma in the mediastinum, whence it was subsequently resected after median sternotomy.

Hence, the initial success rate (defined as postoperative normocalcemia (serum calcium between 2.20-2.60 mmol/L) on day one) was 98% (120/123) in MIA and 95% (42/44) in CNE (NS). Until today (median follow-up 41.5 months, IQR 22-52) no recurrent disease has been documented.

Table 1 Patient characteristics.

	MIA		CNE	
Patients (n)	123		41	
Age (years)	59		60	
Male / Female	37/86	(30/70%)	12/29	(29/71%)
Asymptomatic (n)	92	(75%)	29	(71%)
Symptoms (n)	31	(25%)	12	(29%)
Nephrolithiasis	17		8	
Bone pain	10		4	
Abdominal complaints	3		2	
Miscellaneous	12		4	
Serum calcium *				
Preoperative (mmol/L)	2.84	(2.35-3.60)	2.85	(2.50-3.88)
Postoperative (mmol/L)	2.25	(1.61-2.80)	2.29	(1.81-2.64)
Preoperative PTH † (pmol/L)	12.5	(4.9-180)	13.1	(9-234)

MIA minimally invasive adenomectomy.

CNE conventional neck exploration.

* Serum calcium normal 2.20-2.60 mmol/L.

† Preoperative PTH normal <8 pmol/L.

Resources and costs

Resources could be determined for all patients and are listed in **Table 2**.
The median operation time was 20 minutes (IQR 15-25) for MIA and 75 minutes (70-90) for CNE ($p<0.0005$). Median additional time in the operation room (time in the operation room minus exploration time) for preoperative and postoperative anesthetic care was 42 (36-50) minutes for MIA versus 40 (29-54) minutes for CNE. No significant difference ($p<0.808$) was measured in median recovery time between MIA (115 minutes) and CNE (117 minutes), whereas median admission was significantly shorter ($p<0.0005$) in MIA (2 days) versus CNE (3days).
Owing to surgical failure, vocal cord paralysis or clinically significant hypocalcemia, 30 additional consultations (15 in both groups, 12% MIA and 34% CNE) were necessary, 32 additional laboratory tests for serum calcium were performed, and 11 patients needed supplementary calcium. Failure after MIA resulted in re-exploration on the same day in three patients. Three other failures in the MIA group underwent re-exploration during a second admission. Two of them had additional Sestamibi scintigraphy before being re-explored. As a consequence, a total of 380 minutes of exploration time and 9 admission days were added to the MIA group. Two failures in the CNE group were responsible for 165 additional operative

Table 2 Measurement of resources.

	MIA	CNE
Pre-admission phase		
Consultation	123	41
Ultrasonography	123	41
Computed tomography	90	36
MIBI	0	2
Admission phase		
Operative time (average in min)	20	70
Additional time in operation room (average in min)	42	40
Recovery time (average in min)	115	117
Hospital days (average in days)	2	3
Perioperative PTH assay	57	24
Laboratory tests	123	41
Post admission phase		
Consultation	138	56
Recurrent disease	0	0
Complications (miscellaneous)	0	0
Laboratory tests	136	55
Complications		
Conversion	4	0
Additional imaging US	2	0
CT	0	0
MIBI	2	2
Reexploration	6	2
Operative time (average in min)	63	83
Additional time in operation room (average in min)	43	45
Recovery time (average in min)	108	140
Hospital stay (average in days)	3	8.5
Perioperative PTH assay	4	2
Laboratory tests	3	2
Temporary hypocalcemia	5	6
Miscellaneous temporary vocal cord paralysis	2	1
Bleeding/infection	0	0

Data are given in numbers, unless stated otherwise.

Table 3 Cost of main resources (Euro's).

	MIA	CNE
Consultation	10,659	3,962
Imaging	19,311	8,824
Surgical supplies	13,070	4,357
Anesthetic supplies	5,582	1,861
Recovery room supplies	391	130
Personal operation cost	9,373	10,190
Personal perioperative period cost	7,010	2,264
Personal recovery cost	6,677	2,297
Hospital stays	75,878	42,960
Perioperative PTH assay	1,467	625
Laboratory tests	1,783	667
Additional cost of complications	7,203	8,177
Total costs from hospital perspective	*158,404*	*86,314*
Average cost per patient (+/- SD)	**1,288 +/- 431**	**2,106 +/-1070**

minutes and 17 extra days in hospital, 12 of these days being attributable to the patient who had sternotomy. Both these patients had US and Sestamibi scintigraphy in their work-up before reexploration.

Resources were multiplied by unit costs to obtain total costs. **Table 3** shows the costs for preoperative work-up, operation and admission costs, complications and postoperative follow-up for both groups. Mean total costs (+/- SD) were calculated to be € 1,288 +/- 431 for MIA and € 2,106 +/- 1070 for CNE ($p<0.0005$).

Sensitivity analyses

The analysis for MIA shows that an increase in average total costs of 63% would result in a break-even point for total hospital costs (**Table 4**).

The first sensitivity analysis revealed that operation time of MIA may increase (with 1460%) to 272 minutes before the costs of MIA equal those of CNE.

Similarly a prolongation of 2.5 days (225%) of admission time in MIA would equal total costs of both methods. If, theoretically, admission for CNE would be reduced to one day, total average cost would decrease to € 1,377 (7% more expensive than MIA).

From the third analysis it can be calculated that the maximum allowable failure rate for MIA is 54%. This is based on recorded resources of failed MIA and the calculation that the average costs for reexploration in MIA is € 1,491 per reexplo-

Table 4 Sensitivity analyses. Effects on total average costs in minimally invasive adenomectomy and conventional neck exploration after changing appreciable variables.

Analysis	Variable	Variation	Effect		
			%	€	in terms
BE	average MIA costs	increase by	+ 63	2,106	MIA cost equals to CNE cost
1	operating time	increase of 272 minutes in MIA	+ 1460	2,106	MIA cost equals to CNE cost
2	admission	increase of 2,5 days in MIA	+ 225	2,106	MIA cost equals to CNE cost
		reduction to 1 day in CNE	- 35	1,377	CNE cost reduces to 107 % of MIA cost
3	failure rate	67 failures in MIA	+ 54	2,106	MIA cost equals to CNE cost
4	imaging	CNE minus imaging costs	- 10	1,890	CNE cost reduces to 147 % of MIA cost
		imaging costs CNE allocated to MIA	+ 6	1,360	MIA cost increases with 6%; CNE cost 139 % of MIA
5	PTH assay	MIA plus PTH assay	- 4	1,242	MIA cost reduces with 4 %
		CNE plus PTH assay	- 6	1,977	CNE cost reduces with 6 %

BE = break-even.

ration, indicating that average total costs of MIA and CNE are equalized after 67 (67/123) failed MIA procedures.

Our fourth sensitivity analysis calculated costs of CNE in our series disregarding imaging costs. After deducting total imaging costs, the total average cost for CNE reduces to € 1,890 (reduction of 10%). If all imaging costs are then charged to MIA, costs in MIA rise to an average of € 1,360 (increase of 6%).

Finally, if PTH measurement would be used in every exploration, costs for MIA and CNE become € 1,242 and € 1,977 respectively; a further additional saving of 4 % and 6 % respectively.

Discussion

Conventional neck exploration was found to be more expensive than minimally invasive adenomectomy from a hospital point of view. Three dominant features of the minimally invasive technique that contribute towards the disparity in costs were identified. Firstly, since the exploration is limited to the diseased gland only, operative time is significantly shorter, but well comparable with reported [2 3] exploration times of 25-30 minutes in similar limited access parathyroid surgery.

Secondly, admission time is reduced from three to two days in favor of MIA. However, an admission time of three days, as we found in our study after bilateral exploration, is longer than the admission times of 1.4 to 1.9 days after comparable surgery reported in recent papers [14 15]. Therefore, we recalculated costs, using admission time as a variable in the sensitivity analysis. This showed that a reduction of stay to one day made costs compatible. However, if the assumption is made that admission time in CNE is reduced, it may also concomitantly be reduced in MIA, and thus lead to further cost reduction in the latter group. Furthermore, it should be realized that further cost reduction might be expected from MIA, when executed in day-care setting using intravenous sedation combined with the use of local anesthesia [2].

Thirdly preoperative imaging is a prerequisite to select patients for MIA, but we believe this is defensible because imaging in patients with primary hyperparathyroidism will result in identification of suitable patients for MIA, which is considered to be beneficial for patients with primary hyperparathyroidism. We agree with the statement that imaging is of no added value in first time CNE. Imaging consumed about 12 percent of the total budget in MIA (10 percent in CNE) but it resulted in MIA being performed in 75% (123/164). The fourth sensitivity analysis showed differences of 47 percent and 39 percent in costs between MIA and CNE after imaging costs were firstly denied in CNE and then allocated to MIA.

It is vital to realize that sensitivity analyses change only one variable at a time, whereas in reality this is not the case. For example, if operative time is prolonged with four-and-half hours in MIA, admission time will probably increase as well.

The use of a perioperative parathormone assay as predictor of successful surgical treatment will facilitate 'delayed' conversion the same day when necessary during MIA or continuing exploration after CNE, resulting in limited additional work-up and need for secondary admissions for re-exploration. We calculated in our last sensitivity analysis that the use of perioperative parathormone assay results in an additional cost saving of 4 percent in MIA and 6 percent in CNE. However, even if we calculate total costs for failed MIA, using all records including those of failures before we began to use perioperative parathormone assay, it can be demonstrated that a maximum allowable failure rate of 54 percent in MIA will equalize costs with CNE. This is unlikely to occur and therefore we believe the outcomes of our results are robust.

We did not perform a randomized study. This does not necessarily vitiate the quality of our prospective comparison. Indeed, our groups are well comparable. Effectiveness for instance in terms of quality of life or morbidity and mortality is unlikely to differ between the two procedures. It is therefore completely justifiable to perform a cost-minimisation-analysis instead of a cost-effectiveness-analysis. However, if it had been recorded, post-operative pain might have been less in MIA patients, enhancing patient satisfaction and allowing them to resume normal life and return to work earlier. This would have counted in favor of MIA, and resulted in a larger cost difference from CNE. Furthermore, a hospital perspective was preferred over a societal perspective because societal costs are unlikely to differ between both alternatives.

In conclusion, minimally invasive adenomectomy is cheaper than conventional neck exploration for primary hyperparathyroidism. Given the present development of the standard use of perioperative PTH assay and the trend toward a shorter hospital stay after both procedures, we expect minimally invasive adenomectomy to be a safe, effective and cheap alternative to conventional neck exploration.

References

1 Tibblin S, Bondeson A-G, Bondeson L, Ljungberg O. Surgical strategy in hyperparathyroidism due to solitary adenoma. Ann Surg 1984; 200: 776-784

2 Inabnet WB, Fulla Y, Richard B, et al. Unilateral neck exploration under local anaesthesia: The approach of choice in asymptomatic primary hyperparathyroidism. Surgery 1999; 126: 1004-1009

3 Chapuis Y, Icard P, Fulla Y, et al. Parathyroid adenomectomy under local anaesthesia with intraoperative monitoring of UcAMP and/or 1-84 PTH. World J Surg 1992; 16: 570-575

4 Norman J, Chheda H. Minimally invasive parathyroidectomy facilitated by intraoperative nuclear mapping. Surgery 1997; 122: 998-1004

5 Van Vroonhoven TJMV, van Dalen A. Successful minimally invasive surgery in primary hyperparathyroidism after combined preoperative ultrasound and computed tomography imaging. J Int Med 1998; 243: 581-587

6 Van Dalen A, Smit PC, van Vroonhoven TJMV, et al. Minimally invasive surgery of solitary parathyroid adenomas in patients with primary hyperparathyroidism: role of ultrasonography with supplemental computed tomography. Radiology (in press).

7 Smit PC, Borel Rinkes IHM, van Dalen A, van Vroonhoven TJMV. Direct, minimally invasive adenomectomy for primary hyperparathyroidism. An alternative to conventional neck exploration? Ann Surg 2000; 231: 559-565

8 Smit PC, Thijssen JHH, Borel Rinkes IHM, van Vroonhoven TJMV. Perioperative parathormone assay to ascertain success of surgical treatment of primary hyperparathyroidism. Ned Tijdschr Geneesk 1999; 143: 742-746

9 Robinson R. Costs and cost-minimisation analyses. BMJ 1993; 307: 726-728

10 Liem MSL, Halsema SH, van der Graaf Y, et al. Cost-effectiveness of extraperitoneal laparoscopic inguinal hernia repair: a randomized comparison with conventional herniorrhaphy. Ann Surg 1997; 226: 668-675

11 Rutten-van Mölken PMHM, van Buschbach JJ, Rutten FFH. Costs and effectiveness. A guideline for healthcare evaluation studies. Maarsen: Elsevier Healthcare; 2000

12 Oostenbrink JB, Koopmanschap MA, Rutten FF. Guideline for cost-evaluation studies in healthcare. Amstelveen: Steering Committee on future health scenarios; 2000

13 Farmacotherapeutisch kompas. Amstelveen, The Netherlands; 1997

14 Goldstein RE, Blevins L, Delbeke D, Martin WH. Effect of minimally invasive radioguided parathyroidectomy on efficacy, length of stay, and costs in the management of primary hyperparathyroidism. Ann Surg 2000; 231: 732-742

15 Greene Ak, Mowschenson P, Hodin RA. Is sestamibi-guided parathyroidectomy really cost-effective? Surgery 1999; 126: 1036-1040

Summary and general discussion

10

Introduction

Since the introduction in the 1970s of the unilateral approach in surgery for primary hyperparathyroidism by Wang [1], authors have increasingly been recommending limited forms of parathyroid surgery [2 3]. Although unilateral explorations reduce operation time and admission days, decrease operative risk and give better cosmetic results, the debate about the best surgical treatment for primary hyperparathyroidism has never been settled. 'Bilateralists' oppose less invasive approaches because they estimate the incidence of multiple gland disease to be as high as 30% [4]. However, in spite of a systematic bilateral exploration of the neck in search of the diseased parathyroid gland, with identification and estimation of the size of all parathyroid tissue, in only 44% of cases are four glands identified, in 37% three, and in 19% less than three [5].

In **chapter 1** we reported an exceptional case of persistent hyperparathyroidism (due to a non-descended inferior parathyroid) after extensive bilateral exploration, illustrating a clinical dilemma that can be encountered in parathyroid surgery. Imaging carried out prior to re-exploration and including, among other methods, ultrasonography and computed tomography, revealed a parathyroid adenoma at the level of the mandibular angle and the hyoid bone. Guided by the imaging results the adenoma was successfully resected by a local direct procedure taking less than 10 minutes.

In general, the main reason an adenoma is not found during exploration is the variability in location, rather than variety in the number of glands. It is therefore of pivotal importance to understand not only the anatomy, but also the embryology of the parathyroid glands. As radiologist John Doppman succinctly stated, 'If you are an experienced parathyroid surgeon and not able to find a tumor, you cannot have looked high enough'.

Since primary hyperparathyroidism can be diagnosed with nearly 100% accuracy and successfully treated in more than 95% of cases, surgery is the treatment of choice. The gold standard in parathyroid surgery has been conventional neck exploration (CNE), and with success rates exceeding 95% and virtually no complications nothing more seemed left to be desired. However, it cannot be denied that there is a discrepancy between the extent of the operation and the size of the offending gland in the majority of patients [6]. Encouraged by the pace of development in methods of imaging (resulting in increased accuracy), combined with the knowledge that primary hyperparathyroidism is caused by a solitary adenoma in at least 85% of cases, and our experience of the relatively simple and quick MIA procedure (**chapter 1**) we wondered whether such a direct, minimally invasive strate-

gy could be utilized for the more common cases of primary hyperparathyroidism as well.
For this purpose we formulated the following hypothesis (**chapter 3**): 'A substantial group of patients with primary hyperparathyroidism can be successfully treated by limited access surgery after preoperative localization studies and may thus be spared unnecessary extensive dissection (conventional neck exploration)'.

Minimally invasive adenomectomy

We prospectively tested this minimally invasive approach as an alternative to CNE. In **chapter 4** we described the results of 110 consecutive patients who underwent parathyroidectomy, 84 of whom were selected for minimally invasive adenomectomy (MIA) and 26 for CNE. Operating time was 20 minutes in the MIA group and 80 minutes in the CNE group ($p<0.05$), and admission days were reduced to 1.7 days (MIA group) from 3.0 (CNE group) ($p<0.05$). MIA was shown to be a safe and effective technique with a success rate of 96%, capable of replacing conventional neck exploration in approximately 75% of patients, with virtually no complications. Several other investigators have proposed less invasive strategies as alternatives for CNE, most of which have focused on unilateral neck exploration [3]. True minimally invasive techniques were reported to be feasible, guided by preoperative ultrasonography, in about 40% of cases [8], while others have reported excellent results using intraoperative sestamibi-technetium99m scintigraphy (Sestamibi) parathyroid scanning with a hand-held gamma probe [9]. Though attractive when the neck has to be reoperated on due to failure of an initial exploration, in our opinion the costs associated with the Sestamibi scanning preclude its routine use, as discussed below. Alternatively, some surgeons have advocated endoscopy to achieve minimally invasive adenomectomy in selected patients [10]. Although conceptually elegant, this technique appears difficult to learn and certainly requires more operating time than the direct approach described in this thesis.

Asymptomatic and mildly symptomatic patients

The 1990 National Institute of Health (NIH) Consensus Development Conference arrived at a consensus on the indications for surgical intervention in asymptomatic primary hyperparathyroidism [10]. Among their findings, the panel concluded that the diagnosis of primary hyperparathyroidism does not mandate referral for operative intervention in all cases. Conscientious surveillance was thought to be justified in asymptomatic patients whose calcium levels are only mildly elevated (to < 3.0 mmol/L; normal 2.20-2.60), and whose renal and bone status are close to normal (creatinine clearance reduced not more than 30% and bone mass not more than two standard deviations below those of controls matched for age, sex, and ethnic origin.

Nevertheless, patients with primary hyperparathyroidism have significant functional health status impairment independent of the level of serum calcium [11]. In addition, our experience with MIA has provided us with new arguments for making it the surgical option of choice in asymptomatic and mildly symptomatic patients. In **chapter 5** we advised the following strategy for the asymptomatic or mildly symptomatic patient. When a patient has biochemically proven hypercalcemia with inappropriate levels of parathormone (PTH), localization of the adenoma has to be attempted by Doppler-ultrasonography and computed tomography. When test results unequivocally indicate a solitary adenoma the patient is advised to undergo a minimally invasive procedure. However, if the test results are equivocal or indicate the possibility of multiglandular involvement a conservative policy is advocated. If the disease advances, major symptoms develop and/or the patient fulfills the NIH-guidelines, parathyroid imaging should be repeated before whichever form of operation is indicated.

Imaging

Before the introduction of imaging-guided, minimally invasive parathyroid surgery, the general opinion about preoperative localizing studies was that imaging before initial surgery was not worthwhile. This objection to the routine use of localizing tests was based on 1) inferior sensitivity rates in localizing studies (reaching 85% maximum) when compared with success rates in conventional neck exploration (over 95%); 2) the reduced accuracy of localizing studies in multiglandular disease; 3) an unjustified economic burden because of lack of evidence for the cost effectiveness of imaging studies; and 4) the possibillity of misleading less experienced surgeons [10 12 13 14]. Now, a decade after the NIH meeting, some of these argu-

ments may be viewed critically.
Firstly, most of these studies were carried out retrospectively and none followed a strict protocol. Modern, state-of-the-art imaging modalities and prospective adherence to a strict protocol gives, in our experience, good results. Furthermore, a team approach with a dedicated radiologist and an experienced endocrine surgeon has contributed considerably to the success of direct adenomectomy. In our series ultrasonography gave a sensitivity of 78%, a specificity of 78% and a positive predictive value of 96% (**chapter 6**). Despite the fact that the combined results of ultrasonography and computed tomography moderately improved the sensitivity to 84% (**chapter 4**), the diagnostic use of spiral computed tomography was advised with caution, because of the associated costs and risks of radiation (**chapter 6**). Nevertheless, the routine employment of both techniques can be justified because 1) computed tomography produces an operator-independent roadmap, and 2) with the use of 'cine-loop' reconstruction at the computer work-station, additional information and an essential three-dimensional view are available, helping the surgeon in planning the operation.
Secondly, imaging (in our series ultrasonography combined with computed tomography) was shown to be beneficial in preoperative planning for the treatment of primary hyperparathyroidism since, with its aid, we were able to select approximately 75% of patients for minimally invasive adenomectomy.
Thirdly, economic evaluations were limited in number and, if available, mostly based on bilateral explorations.

On the basis of our personal favorable results we adhered strictly to the use of ultrasonography combined with computed tomography. However, this does not preclude the use of other modalities in the treatment of primary hyperparathyroidism. Parathyroid scanning using radioisotopes has evolved over the years and is able to localize adenomas in approximately 90% of cases [15 16]. The use of a hand-held gamma probe (Sestamibi) to guide the surgeon to the parathyroid adenoma has been advocated as being useful in reoperations on the neck [17]. Moreover, excellent cure rates have also been reported with the use of a gamma probe in initial surgery, simultaneously decreasing operating time and hospital stay, resulting in significant cost reduction without compromising patient safety [9 18]. Conventional scintigraphy (thallium201-technetium-Tc99m pertechnetate scanning) is, in our opinion, not suitable for selecting patients for MIA because of the relatively poor image resolution and anatomical information obtained. Sestamibi, has been reported to give sensitivity rates up to 100% in solitary disease [14], but, in our opinion, it should be restricted to a selected group of patients because of its high costs (+/- € 680). The modest increase in accuracy using Sestamibi does not justify the disproportionate rise in cost.
Other imaging modalities consist of magnetic resonance imaging (MRI) and selective venous catheterization for measurement of PTH levels. Although MRI (sensitiv-

ity 57-90%) is only marginally more accurate than computed tomography (sensitivity 41-86%) [13 19], MRI avoids the need for use of contrast medium and shoulder artifacts are circumvented, we prefer computed tomography for reasons of availability and cost. Finally, since selective PTH sampling requires an expert radiologist, is invasive and associated with high costs, its use should be restricted to reoperations.

Parathormone assay

The clinical utility of rapid PTH measurement in parathyroid surgery was first reported in 1988, using a modified intact PTH immunoradiometric assay [20]. The authors concluded that intraoperative measurement of PTH would be helpful to the surgeon. The combination of more accurate preoperative localization studies and the ability to predict the postoperative serum calcium would facilitate limited explorations [3]. The use of non-radioactive kits transportable on a trolley has allowed the rapid assay to be performed in or adjacent to the operating theatre. These commercially available portable kits measure PTH within 15 minutes with sensitivity rates reaching 96%, specificity of 100% and overall accuracy of 97% [21 22]. Although it cannot be denied that these tests are highly effective providing true intraoperative results, the preliminary procedures (e.g. instrument performance check, generating calibration curves and assay quality control prior to surgery), and their substantial cost preclude their widespread introduction. In a search for a less costly alternative rapid PTH assay, we studied the reliability and applicability of a non-portable rapid PTH assay to predict successful surgical treatment of primary hyperparathyroidism (**chapter 7**). In that chapter we described the results of the first 35 patients measured with a rapid PTH assay (modified Immulite Regular assay) providing results within 70 minutes. Once the results were shown to agree fully with both conventional PTH measurements and postoperative serum calcium levels, we included the Immulite Regular assay in our protocol. We also tested three other non-portable PTH assays (Immulite Turbo, Advantage Regular and Advantage Turbo assays), which are described in **chapter 8**. All these methods were concluded to be useful to ascertain the success of an exploration. The Immulite Regular and Immulite Turbo assays, however, were believed to be more accurate than the Advantage Regular and Advantage Turbo assays when used according to our protocol (a decline in PTH of >50%, measured 8 minutes after resection, predicting normocalcemia).

Costs

Minimally invasive adenomectomy has definitely entered the therapeutic regimens for primary hyperparathyroidism, and therefore it is important to study the economic burden. We cost-analyzed a prospective series of 164 patients to obtain information on the relative costs of MIA and CNE (**chapter 9**). To observe the effect of changing appreciable variables, multiple sensitivity analyses were carried out. The mean cost of MIA was calculated as € 1,288 and that of CNE € 2,106 ($p<0.0005$). The reason MIA is so much cheaper than CNE is the differences in operating time (median 20 minutes in MIA versus 75 minutes in CNE) and admission days (2 days in MIA versus 3 days in CNE). Sensitivity analyses showed that an increase in total average costs of 63%, an increase in operating time to 272 minutes, prolongation of admission from 2 to 4.5 days, or an initial operation failure rate of 54% in the MIA group would result in MIA costs equaling those for CNE. Such extreme examples are clearly unrealistic, but admission time remains a variable that is highly dependent on 'local' logistics, and may be amenable to reduction. In particular, day care surgery will shortly become possible for MIA, provided a safe protocol for the management of postoperative hypocalcemia can be designed (and adhered to).

The future

The ongoing technical developments of imaging modalities presage an increase in discriminating capacity and increasing accuracy of various techniques, making MIA possible for even more patients. The possibility of day-care MIA, using intravenous sedation combined with local anesthesia, will further liberalize the indications for this method.

Conclusion

In conclusion, minimally invasive adenomectomy is a safe and effective alternative to conventional neck exploration, able to replace it in approximately 75% of cases. It is not only associated with a very low complication rate, comparable to that of conventional neck exploration, but is also cheaper than conventional exploration. In the future, additional savings may be anticipated when day-care MIA becomes possible.

References

1 Wang CA. Surgical management of primary hyperparathyroidism. Curr Prob Surg 1985; 22: 1-50

2 Tibblin S, Bondeeson AG, Ljungberg O. Unilateral parathyroidectomy in hyperparathyroidism due to single adenoma. Ann Surg 1982; 195: 245-252

3 Irvin GL III, Prudhomme DL, Deriso GT, et al. A new approach to parathyroidectomy. Ann Surg 1994; 219: 574-581

4 Bruining HA, van Houten H, Juttmann JR, et al. Results of operative treatment of 615 patients with primary hyperparathyroidism. World J Surg 1981; 5: 85-90

5 Van Heerden JA, Grant CS. Surgical treatment of primary hyperparathyroidism: an institutional perspective. World J Surg 1991; 15: 688-692

6 Van Vroonhoven TJMV, van Dalen A. Successful minimally invasive surgery in primary hyperparathyroidism after combined preoperative ultrasound and computed tomography imaging. J Int Med 1998; 243: 581-587

7 Lucas RJ, Welsh RJ, Glover JL. Unilateral neck exploration for primary hyperparathyroidism. Arch Surg; 125: 982-985

8 Chapuis Y, Icard P, Fulla Y et al. Parathyroid adenomectomy under local anesthesia with intraoperative monitoring of UcAMP and/or 1-84 PTH. World J Surg 1992; 16: 570-575

9 Goldstein RE, Blevins L, Delbeke D, Martin WH. Effect of minimally invasive radioguided parathyroidectomy on efficacy, length of stay, and costs in the management of primary hyperparathyroidism. Ann Surg 2000; 231: 732-742

10 Consensus Development Conference Panel. Diagnosis and management of asymptomatic hyperparathyroidism: consensus development conference statement. Ann Int Med 1991; 114: 593-597

11 Burney RE, Jones KR, Christy B, Thompson NW. Health status improvement after surgical correction of primary hyperparathyroidism in patients with high and low preoperative calcium levels. Surgery 1999; 125: 608-614

12 Roe SM, Burns P, Graham LD, et al. Cost-effectiveness of preoperative localization studies in primary hyperparathyroidism disease. Ann Surg 1994; 219: 582-586

13 Miller DL. Preoperative localization and interventional treatment of parathyroid tumors: when and how? World J Surg 1991; 15: 706-715

14 Casas AT, Burke GJ, Mansberger AR jr, Wei JP. Impact of technetium-99m sestamibi localization on operative time and success of operations for primary hyperparathyroidism. Am Surg 1994; 60: 12-16

15 Thulé P, Tharoke K, Vasant J, et al. Preoperative localization of parathyroid tissue with technetium-99m sestamibi 123I substraction scanning. J Clin Endocrinol Metab 1994; 78: 77-82

16 Denham DW, Norman J. Cost-effectiveness of preoperative sestamibi scan for primary hyperparathyroidism is dependent solely upon the surgeon's choice of operative procedure. J Am Coll Surg 1998; 186: 293-305

17 Norman J, Denham D. Minimally invasive radioguided parathyroidectomy in the reoperative neck. Surgery 1998; 124: 1088-1093
18 Chen H, Sokoll LJ, Udelsman R. Outpatient minimally invasive parathyroidectomy: a combination of sestamibi-spect localization, cervical block anesthesia, and intraoprative parathyroid hormone assay. Surgery 1999; 126; 1016-1021
19 Krubsack AJ, Wilson SD, Lawson TC, et al. Prospective comparison of radionuclide, computed tomography and sonographic localization of parathyroid tumors. World J Surg 1986; 10: 579-585
20 Nusbaum SR, Thompson AR, Hutcheson KA, et al. Intraoperative measurement of parathyroid hormone in the surgical management of hyperparathyroidism. Surgery 1988; 104: 1121-1127
21 Irvin III GL, Deriso III GT. A new, practical intraoperative parathyroid hormone assay. Am J Surg 1994; 168: 466-468
22 Boggs JE, Irvin GL III, Molinari AS, Deriso GT. Intraoperative parathormone monitoring as an adjunct to parathyroidectomy. Surgery 1996; 120: 954

Samenvatting (voor de niet ingewijde)

11

Introductie

In de hals, net achter de schildklier, liggen de vier bijschildklieren. Deze kliertjes maken het parathormoon (PTH), dat van invloed is op de kalkhuishouding van het lichaam. Wanneer één (of meerdere) bijschildklier (en) te snel gaat (gaan) werken, wordt deze groter (adenoom) en maakt te veel PTH met als gevolg een stijgend kalkgehalte in het bloed. Dit ziektebeeld heet primaire hyperparathyreoïdie (pHPT) en gaat bij ongeveer 30-40 % van de patiënten gepaard met de volgende klachten: urinestenen, pijn in de botten, verminderd algemeen welzijn (moeheid, verminderde eetlust, depressie), buikklachten en obstipatie. Een sterk verhoogd kalkgehalte kan zelfs levensbedreigend zijn.

De therapie voor deze ziekte is chirurgisch waarbij het adenoom wordt verwijderd teneinde het kalkgehalte in het bloed te normaliseren. De klassieke operatie hiervoor is de conventionele hals exploratie, een procedure waarbij via een ongeveer 12 cm grote incisie in de hals, alle vier de bijschildklieren worden opgezocht, door de chirurg worden beoordeeld op grootte (en dus functie), waarna het adenoom wordt verwijderd. Deze procedure duurt ongeveer anderhalf uur, is uitermate succesvol (tenminste 95% genezing), veilig (weinig complicaties) en gaat gepaard met een ziekenhuis opname van 2 tot 3 dagen.

Bij tenminste 85% van de patiënten met pHPT is maar één bijschildklier ziek (en zijn er drie gezond). Wanneer de chirurg vóór operatie zou weten om welke klier het gaat, zou hij/zij kunnen volstaan met het opzoeken en verwijderen van alleen deze klier. Dan worden de gezonde klieren niet meer opgezocht met als gevolg een beperktere ingreep waardoor 1) de operatie duur korter wordt, 2) patiënten eerder het ziekenhuis verlaten en 3) het litteken kleiner wordt.
In **hoofdstuk 1** wordt een casus beschreven waarbij, ondanks een zeer uitgebreide operatie uitgevoerd door een zeer ervaren chirurg, het adenoom niet kon worden gevonden. Bij deze operatie werden drie gezonde klieren gevonden, maar de vierde (en dus zieke) kon ondanks alle inspanningen niet worden geïdentificeerd. Na de ingreep bleef het kalk in het bloed verhoogd, waarop de patiënt werd doorverwezen naar het Universitair Medisch Centrum in Utrecht. In een poging het adenoom preoperatief in beeld te brengen (localiseren) werd (onder andere) een echografie en CT van de hals verricht. De radioloog vond bij echografie het adenoom op een zeer ongebruikelijke plek, hoog in de hals. Nadat dit werd bevestigd met CT onderzoek kon het adenoom op betrekkelijk simpele wijze, via een incisie van anderhalve cm in minder dan 10 minuten, worden verwijderd.

Aangemoedigd door deze ervaring, de wetenschap dat in tenminste 85% van de gevallen de ziekte wordt veroorzaakt door maar één adenoom en het gegeven dat de kwaliteit van beeldvormende technieken sterk is verbeterd, ontwikkelden wij een beperkte, minimaal invasieve operatie techniek voor patiënten met pHPT.

In **hoofdstuk 3** werd de volgende hypothese geformuleerd 'Bij een substantieel aantal patiënten met pHPT kan, na preoperatieve beeldvorming worden volstaan met een minimaal invasieve verwijdering van het bijschildklier adenoom waardoor een onnodig grote ingreep (conventionele hals exploratie) wordt vermeden'.

Minimaal invasieve bijschildklier chirurgie

In **hoofdstuk 4** beschrijven we de resultaten van de eerste 110 patiënten die we in de periode oktober 1994 tot oktober 1998 opereerden voor pHPT. Na beeldvorming (echografie en CT) werden vierentachtig (76%) patiënten geselecteerd voor de minimaal invasieve ingreep, 26 voor de conventionele ingreep. De mediane duur van de minimaal invasieve ingreep was 20 minuten versus 80 minuten ($p<0,05$) bij de conventionele ingreep. De mediane opnameduur reduceerde van 3,0 dag (conventionele groep) naar 1,7 dag ($p<0,05$). Het succes percentage (gedefinieerd als postoperatieve normalisatie van het kalkgehalte in het bloed, gemeten op de eerste dag na operatie en bevestigd 1 week en 1 maand na operatie) was 96%. De minimaal invasieve ingreep was even veilig als de conventionele ingreep.

De niet symptomatische en mild symptomatische patiënt

Consensus over indicaties voor chirurgisch ingrijpen bij pHPT werd bereikt op de 'National Institute of Health (NIH) Consensus Development Conference on Primary Hyperparathyroidism', welke werd gehouden in 1990 (Verenigde Staten). Eén van de conclusies die werd getrokken was dat niet alle patiënten in aanmerking kwamen voor chirurgie, maar dat chirurgisch ingrijpen gerechtvaardigd is indien 1) het kalkgehalte in het bloed een bepaalde grens passeert (>3,00 mmol/L), 2) er sprake is van (evidente) klachten, 3) er door de ziekte een bepaalde mate van botontkalking optreedt of 4) de nierfunctie als gevolg van de ziekte verslechtert (beneden een bepaalde grens). Een afwachtend beleid werd geadviseerd indien niet aan (één van) de criteria wordt voldaan.

Met de introductie van de minimaal invasieve ingreep verdwijnt echter een aantal nadelen van operatie. Immers, vergeleken met de conventionele ingreep is de minimaal invasieve ingreep kleiner en dus minder belastend voor de patiënt. Dit in combinatie met het feit dat een verhoogd kalkgehalte in het bloed de gezondheid op den duur ten nadele beïnvloedt en de vraag (die velen zich stellen) of patiënten zonder enige symptomen werkelijk bestaan (met andere woorden iedereen met de ziekte heeft klachten maar is zich daarvan niet altijd bewust omdat 1) de klachten vaag zijn en 2) ze langzaam zijn ontstaan), pleiten voor een meer liberaal beleid ten aanzien van chirurgische therapie. In **hoofdstuk 5** wordt, voor die patiënten die geclassificeerd worden als a-symptomatisch of weinig symptomatisch de volgende strategie voorgesteld; Nadat de diagnose pHPT is gesteld ondergaat de patiënt localiserend onderzoek (echografie en CT). Wanneer er (zonder twijfel) sprake is van één adenoom wordt de patiënt gepland voor de minimaal invasieve methode. Wordt het adenoom bij beeldvorming niet gevonden, of bestaat er onzekerheid of een in beeld gebrachte afwijking een adenoom danwel een andere structuur is, of indien er sprake is van meerdere adenomen (dus een conventionele ingreep moet worden uitgevoerd) wordt een terughoudend beleid gevoerd. Indien de ziekte vervolgens verslechtert (b.v. verergering van de symptomen, kalkgehalte stijgt boven 3,00 mmol/L), wordt de patiënt opnieuw aangeboden voor beeldvorming gevolgd door chirurgisch ingrijpen.

Preoperatieve beeldvorming

De opinie over het nut van beeldvorming voorafgaand aan bijschildklier chirurgie (conventionele hals exploratie) was, vóór de introductie van minimaal invasieve methoden, dat het geen additionele waarde had om het succes van de ingreep te garanderen. De motivatie hiervoor was dat 1) de gevoeligheid van de beeldvormende technieken (sensitiviteit maximaal 85%) lager was dan het succes van de conventionele ingreep (tenminste 95% zonder preoperatieve beeldvorming), 2) de gevoeligheid verder afnam wanneer er sprake was van meer dan één adenoom, 3) bewijzen voor kosten effectiviteit van beeldvorming ontbraken en 4) beeldvorming de minder ervaren chirurg op het verkeerde been kon zetten.

Deze feiten waren echter gebaseerd op 1) retrospectief materiaal en 2) resultaten behaald met (inmiddels) verouderde apparatuur. Het gebruik van nieuwe ‘state of the art’ apparatuur, goede communicatie tussen radioloog en chirurg en een degelijk prospectief protocol leidt (in onze ervaring) tot de volgende resultaten; selectie voor minimaal invasieve chirurgie bij ongeveer driekwart van de patiënten, sensitiviteit en specificiteit van echografie 78%, positief voorspellende waarde 96% (**hoofdstuk 6**). Hoewel de sensitiviteit van echografie en CT samen iets hoger ligt (84%) (**hoofdstuk 4**) zijn er argumenten voor en tegen het routinematig gebruik van CT die in dit proefschrift worden bediscussieerd. Als tegenargumenten worden in **hoofdstuk 6** genoemd de stralenbelasting voor de patiënt en de additionele kosten die worden gemaakt terwijl de resultaten maar weinig verbeteren. Echter, in tegenstelling tot echografie, zijn de resultaten van CT ‘onderzoeker onafhankelijk’ en kan met behulp van de computer (easy-vision werkstation) een goed driedimensionaal beeld worden verkregen van het gescande gebied (**hoofdstuk 4**).

Peroperatieve parathormoon bepalingen

Het succes van een ingreep wordt afgemeten aan een postoperatief normaal kalkgehalte in het bloed. Nadat het adenoom is verwijderd daalt het kalkgehalte langzaam (ongeveer 24 uur) naar normaal waarden. Om te weten of een ingreep is geslaagd (en de patiënt is genezen) moet dus tot de volgende dag worden gewacht. Wanneer een tweede adenoom bij beeldvorming wordt gemist zal deze bij een minimaal invasieve ingreep niet worden verwijderd met als resultaat persisterende ziekte. Dan zal de patiënt op een later tijdstip een tweede operatie (in eventueel) tweede opname moeten ondergaan. Om dit probleem te ondervangen is een controle van chirurgisch handelen wenselijk. Wanneer een dergelijke test persisterende ziekte voorspelt kan vervolgens in dezelfde sessie verder geëxploreerd worden (conventionele exploratie) om het tweede (derde of vierde) adenoom te verwijderen.

De halfwaarde tijd van het PTH is zeer kort (ongeveer 3 minuten). De PTH concentratie in het bloed zal dus, nadat het adenoom is verwijderd, snel dalen.
Door PTH spiegels van voor en na operatie te vergelijken kan een uitspraak worden gedaan of al het te snel werkend weefsel is verwijderd. Een cito (snel) uitgevoerde PTH meting kan dus als de gewenste snelle controle dienen.
Het meten van dit hormoon op klassieke wijze neemt echter vele uren in beslag en is derhalve niet geschikt als chirurgische controle. In **hoofdstuk 7** worden de resultaten beschreven van een gemodificeerde PTH meetmethode (Immulite Regular assay) die binnen 70 minuten resultaten levert en getest werd op betrouwbaarheid en bruikbaarheid als gewenste voorspeller van chirurgisch handelen. Nadat deze cito PTH assay betrouwbaar bleek als chirurgische controle (100% correlatie tussen PTH test en postoperatief kalkgehalte), werd het geïntegreerd in ons protocol.
Voor dit doel zijn verschillende cito PTH assays commercieel verkrijgbaar. Enkele van deze kunnen worden verricht op de operatiekamer (portable assays) in plaats van in het laboratorium (non-portable assays), met als voordeel dat geen (kostbare) tijd gaat verloren bij het transport van de bloedsamples van operatiekamer naar laboratorium. Deze assays leveren weliswaar zeer snel (binnen 15 minuten) test uitslagen, waardoor een echte intra-operatieve test ontstaat, ze zijn ook (buiten proportioneel) duur (ongeveer 1.000 US dollar per patiënt).
Als alternatief voor deze 'dure' PTH assays testten wij vier (ongeveer 100 US dollar per patiënt) (non-portable) laboratorium assays: Immulite Regular (test resultaten <70 minuten, Immulite Turbo (test resultaten <20 minuten), Advantage Regular (test resultaten <35 minuten) en Advantage Turbo (test resultaten <20 minuten).
In **hoofdstuk 8** worden de resultaten van deze vier verschillende PTH testen beschreven. Alle vier testen waren geschikt als snelle controle, echter de Immulite Regular en Immulite Turbo assays waren in onze ervaring en wanneer getest volgens de richtlijnen van ons protocol (dwz dat een PTH daling van meer dan 50% moet zijn opgetreden wanneer 8 minuten na verwijdering van het adenoom het

bloed wordt afgenomen en getest), nauwkeuriger dan Advantage Regular en Advantage Turbo.

Kosten

In hoofdstuk 9 worden de resultaten van een kostenminimeringsanalyse en verscheidene (univariate) gevoeligheidsanalyses beschreven. De gemiddelde kosten voor de minimaal invasieve ingreep werden berekend op 1.288 Euro per patiënt versus 2.106 Euro voor de conventionele ingreep. Met name het verschil in operatietijd en opnameduur tussen beide methoden was verantwoordelijk voor dit prijsverschil. Pas wanneer de operatieduur van de minimaal invasieve methode wordt verlengd tot 272 minuten, of de opnameduur wordt verlengd tot vier en een halve dag, of 54 % van alle minimaal invasieve ingrepen mislukt, worden de kosten van de minimaal invasieve methode gelijk aan die van de conventionele methode.

De toekomst

Verdere verbeteringen op het gebied van beeldvormende technieken zullen resulteren in toenemende gevoeligheid en een groter onderscheidend vermogen waardoor, in de toekomst, meer patiënten met pHPT geselecteerd kunnen worden voor minimaal invasieve chirurgie. Dit in combinatie met de mogelijkheid patiënten in dagopname onder lokaal anaesthesie te opereren zal bijdragen aan verdere liberalisatie van indicatie voor chirurgisch ingrijpen

Conclusie

Minimaal invasieve bijschildklier chirurgie is even veilig en goed als de conventionele hals exploratie. Het vervangt de conventionele hals exploratie bij driekwart van alle patiënten met pHPT, is goedkoper waarbij in de toekomst verdere kostenbesparing mag worden verwacht wanneer de ingreep zal worden uitgevoerd in dagbehandeling.

Dankwoord

Het schrijven van een proefschrift is onmogelijk zonder de hulp en inspanningen van velen. Aan allen ben ik veel dank verschuldigd, een aantal wil ik met name noemen;

Prof. dr Th.J.M.V. van Vroonhoven.
Beste professor, bij u promoveren, nota bene op het gebied van de bijschildklieren ervaar ik als een groot voorrecht en genoegen. Ik ben u niet alleen dankbaar voor uw begeleiding bij mijn promotie maar zeker ook voor uw aandeel en betrokkenheid in zowel mijn opleiding tot algemeen chirurg als in het dagelijks leven.

Drs. A. van Dalen.
Beste Bert, jij als de andere 'architect' van bijschildklier chirurgie 'nieuwe stijl' hebt met je streven naar perfectie een belangrijk aandeel in dit geslaagde project. Ik heb met plezier met je samengewerkt en ben je dankbaar voor je tomeloze inzet die heeft geleid tot mijn promotie.

Dr I.H.M. Borel Rinkes.
Beste Inne, eindelijk is het dan zover. Regelmatig zaten we naast elkaar, we spraken dan honderd-uit en behalve over de wetenschappelijke vorderingen met name veel over 'van die dingen in het leven'. En behalve dat ik dit iedere keer weer onwaarschijnlijk gezellig vond/vindt, wist je me telkens weer, gewapend met frisse moed de goede kant op 'te duwen'. Inne, veel dank, zowel voor je wetenschappelijke inbreng als voor je vriendschap !

Prof. dr Chr. van der Werken.
Beste professor, op uw vraag 'wat kom je doen' (8 januari 1996, 07.15 uur) kan ik nu een beter antwoord geven dan toen: 'promoveren en chirurg worden, professor'. Dank voor uw betrokkenheid (en geduld) gedurende mijn AZU jaren.

De overige leden van de beoordelingscommissie.
Prof. dr C.J.M. Lips, prof. dr J.H.H. Thijssen en prof. dr E.E. de Lange voor uw interesse, betrokkenheid, enthousiasme en bijdragen die hebben geleid tot dit proefschrift.

De afdeling Radiologie van het UMCU en met name de echolaboranten die mij telkens weer trouw belden wanneer weer een echo werd gemaakt.

De medewerkers van het endocrien laboratorium. Jullie enthousiasme, vakkundigheid en betrokkenheid zijn de sleutel van het succes van peroperatieve PTH's. Met name wil ik John van Zon, Inge Maitimu en Hilda Compagner danken voor hun inspanningen die hebben geleid tot de ontwikkeling en realisatie van peroperatieve PTH metingen.

De afgelopen jaren heb ik samengewerkt met een groot aantal medeassistenten in zowel het Universitair Medisch Centrum Utrecht als het Diakonessenhuis Utrecht. Dankzij jullie collegialiteit heb ik de ruimte gehad die nodig was om deze studie te voltooien. Niet alleen hiervoor ben ik jullie veel dank verschuldigd, maar ook voor alle geleverde inspanningen (zoals het coördineren van PTH's) en bovenal de prima tijd die ik met jullie had / heb.
Eén ster aan het firmament wil ik met naam noemen en danken voor zijn inspanningen rond de PTH coördinatie: Bram Fioole bedankt.

Dr M.S.L Liem.
Beste Mike, het was goed zaken met je doen. Je wetenschappelijke kwaliteiten bewezen zich maar al te vaak bij de kostenanalyse die we hebben uitgevoerd. Hoewel je op dit gebied absoluut 'superieur' bent kan ik je aanraden in de toekomst wat beter naar mij te luisteren wanneer het gaat over 'beurs bewegingen'. Alleen dan kan je pakket 'robust' van karakter worden.

I would like to thank Hugh and Amanda de Glanville for their effort in revising parts of this thesis.

Dr H.F. Veen.
Beste dr Veen, uw aandeel is groot. Niet alleen vanwege het leveren van Rotterdamse patiënten aan de 'para' studie, maar zeker ook vanwege uw interesse en betrokkenheid in de opleiding, promotie en bovenal het leven van Smit daarbuiten. De vele telefoontjes, de Ikazia bezoeken en het jaarlijks terugkerend ritueel binnen 'de schoonste der schoone' dragen bij aan het 'senang'. Dr Veen, waarvoor dank !

Mw C.K. Schoen-Obbink.
Lieve TT, niet voor niets draag ik dit proefschrift onder andere aan u op. De liefde waarmee u (en Rutger Jan, Michiel en Caroline -plus aanhang-) de gebroeders Smit (en Sanne) heeft opgenomen in de Schoenen familie is groots en is van onschatbare waarde. Het is een voorecht mensen als u als voorbeeld te hebben in het leven. Lieve TT, dank.

Tijs en Jelke Smit
Lieve broeders, dank voor jullie zorg, geduld en nimmer aflatende steun.
Wordt het niet eens tijd dat jullie een feestje gaan geven ?

En natuurlijk mijn lieve Sanne. Mijn stralende zonnetje. En dat zie ik zo graag. Want stralen kun je zo goed, dus blijf dat nog maar héél lang doen. Lief, dank je voor de eerste 10.

Curriculum Vitae

De schrijver van dit proefschrift werd geboren op 18 januari 1968 te Vlissingen. Hij volgde zijn middelbare schoolopleiding aan het Eerste Vrijzinnig Christelijk Lyceum te Den Haag, alwaar hij in 1986 zijn HAVO diploma behaalde, om vervolgens in 1987 zijn VWO diploma te halen aan het Noctua college te Den Haag. Dit zelfde jaar werd met de studie Geneeskunde aan de Erasmus Universiteit Rotterdam begonnen. Na het behalen van het artsexamen in december 1995 werkte hij vanaf januari 1996 als arts-assistent niet in opleiding op de afdeling heelkunde van het Academisch Ziekenhuis Utrecht. Medio 1997 werd begonnen met het onderzoek, hetgeen geleid heeft tot dit proefschrift. In januari 1998 werd in het Academisch Ziekenhuis Utrecht gestart met de opleiding tot algemeen chirurg (opleider: prof. dr Th.J.M.V. van Vroonhoven). Sinds januari 2001 volgt hij de laatste drie jaar van zijn chirurgische opleiding in het Diakonessenhuis te Utrecht (opleider: dr G.J. Clevers).