

# Minimally Invasive Parathyroidectomy in Primary Hyperparathyroidism : A Mini-Review



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## Abstract

In this mini-review the evolution of minimally invasive parathyroidectomy (MIP) in patients with primary hyperparathyroidism (PHP) during the last two decades, is discussed. Old and new localization techniques for identifying parathyroid adenomas, including high-resolution ultrasound, sestamibi scanning and its SPECT/CT modifications, intraoperative PTH measurements (IOPTH) and radioguided parathyroidectomy are reviewed. Ultrasound and conventional sestamibi scanning result in a correct localization in 85% of patients. MIP results then in 98-99% cure rates in PHP patients. This 30-45 minutes procedure can be performed as a daycase care, even under local anesthesia, without sedation. Cosmesis is optimal, operating time, length of hospital stay, costs and postoperative temporary hypocalcemia are reduced by 50%, compared to conventional bilateral neck exploration. The fear of recurrent laryngeal nerve damage caused a shift from the general surgeon to the ENT surgeon, as the preferred endocrine neck surgeon. This has been proven unfairly, as recurrent laryngeal nerve damage is extremely rare in MIP. There is no place for SPECT/CT sestamibi scanning, CT and 3-or 4 dimensional CT or MRI in the initial diagnostic work-up of PHP patients. Exclusion of these modalities from routine parathyroid imaging protocols, saves the patient from unnecessary radiation exposure and imaging time. In 20 years MIP has been settled definitely, as the procedure of first choice in the surgical management of patients with primary hyperparathyroidism.

**Abbreviations:** MIP: Minimally Invasive Parathyroidectomy; PHP: Primary Hyperparathyroidism; MIVAT: Minimally Invasive Video-Assisted Thyroidectomy; MIVAP: Minimally invasive video-assisted parathyroidectomy; BNE: Bilateral Neck Exploration; PTH: Excessive Parathyroid Hormone.

## Introduction

Since the late 1980's, when the first laparoscopic cholecystectomies were performed, minimally invasive surgical techniques have gained interest among all surgical specialties. Endoscopic surgery has been limited to procedures performed in the thorax and abdominal cavity for a long time, because these areas have a pre-existing cavity or space in which to work. It was in the late 1990's, when minimally invasive video-assisted thyroidectomy (MIVAT) was introduced in clinical practice by Miccoli et al. [1]. Minimally invasive video-assisted parathyroidectomy (MIVAP) followed soon [2]. Now, 20 years later the development of various ultrasound-guided and endoscopic video-assisted and robotic surgical techniques have changed the approach to thyroid and parathyroid diseases. In this mini-review the various techniques, selection of patients, preoperative imaging studies, intra-operative parathyroid gland identification and parathyroid hormone sampling, results and complications in PHP patients, as well as the shift to the ENT surgeon as an endocrine neck surgeon will be discussed. Finally the cost-benefit analysis will be considered.

## Minimally Invasive Parathyroid Surgery (MIP)

a) Localization studies: Bilateral neck exploration (BNE) with the identification of at least 4 parathyroid glands and removal of pathological parathyroid tissue has been the standard treatment for more than 60 years. These operations had a cure rate of more than 95%, with a morbidity less than 3% [3]. Most primary hyperparathyroidism (PHP) patients (85%) have a single parathyroid adenoma, responsible for excessive parathyroid hormone (PTH) production [4]. If this could be located correctly parathyroid adenectomy is an ideal candidate for an unilateral surgical approach. Localization studies were performed in the last century, with the use of thallium-technetium subtraction scans. Parathyroid imaging was useful in 50% of cases and less effective in demonstrating multiple gland hyperplasia [5].

Although the indication for parathyroidectomy is settled by the clinical symptoms and biochemical evaluation, new localization techniques, as high-resolution ultrasound (HR-US), sesta [6] MIBI (Methoxyisobutyl Isonitrile) scintiscan and the introduction of

the rapid intra-operative PTH (IOPTH) assay gave a push to the development of MIP [6-8]. Surgeons prefer to have a localization study before an operation. They are not satisfied by having referred a patient with just a biochemical diagnosis of PHP.

## High-resolution ultrasound in PHP

HR-US represents together with nuclear medicine imaging, a reliable first line modality for preoperative localization of a parathyroid adenoma. Neck-US is performed with a high-frequency (7, 5-15 MHz) transducer to enhance spatial resolution, allowing detection of glands larger than 5 mm [9]. Colour-Doppler assessment is a useful integration for the distinction of parathyroid adenomas from other cervical lesions, thus reducing false-positive findings [10]. HR-US has a sensitivity of around 85% in experienced hands [11]. HR-US is mostly combined with sestamibi scintigraphy. Smith et al. evaluated this combination in preoperative localization for parathyroid surgery (n=220). Preoperative ultrasonography, sestamibi scintigraphy or both were obtained in 77%, 93% and 69% of the patients respectively. Preoperative ultrasonography and sestamibi scintigraphy localized an abnormality in 71% and 79% of the patients respectively. Accuracy of localization was 82% for US and 85% for sestamibi scintigraphy. In patients with inaccurate ultrasound localization, the sestamibi scintigraphy correctly identified the site of disease in only 45%. In patients with a non localizing ultrasound, sestamibi scintigraphy was able to localize disease in only 47%, with two adenomas being in the mediastinum [11].

## Sestamibiscan and sestamibi-SPECT/CT

MIBI scanning (double phase) is still the favourite procedure for localizing parathyroid adenomas, including double adenomas and ectopic mediastinal adenomas. MIBI scanning reaches a sensitivity of 90%, when combined with SPECT (single-photon emission computed tomography) or SPECT/CT. Studies comparing newer tracers, such as <sup>11</sup>C-methionine and CT techniques are small however, allowing no other conclusion than that techniques are very expensive and are not standardized, yet. Their value above conventional sestamibi scintigraphy in combination with cheap ultrasound is not proven [12]. In a pooled meta-analysis of 23 studies (n=1236) the detection rate of <sup>99m</sup>Tc-MIBI SPECT/CT in the preoperative planning of patients with PHP was 88% (95%CI; 84%-92%) and 88% on a per patient per lesion-based analysis, respectively [13]. This is not much better, than the sensitivity of sestamibi scintigraphy alone [11]. Gayed et al. could not find an additional benefit of SPECT/CT in identifying diseased parathyroid glands (n=48). Exclusion of the CT part from the routine parathyroid imaging protocol saves the patient from unnecessary radiation exposure and imaging time [14].

## Unilateral MIP

Most surgeons favour a minimally invasive parathyroidectomy. The frequency of multiglandular disease is however still a matter of debate, ranging from 5% in small series up to 30% in large series of parathyroidectomy. Probably this reflects a referral bias [15-

17]. Peel et al. [16] could discharge 101 of 154 patients the same day after performing an unilateral MIP. Reasons for an overnight hospital were distance and available home care. Anesthesia could be administered locally in combination with short i.v sedation, cosmesis was fine with a 2-4 cm incision and hospital costs and operating time were reduced by 50% [16]. A Mayo Clinics cohort analysis of 1361 patients showed equally cure rates for MIP and conventional bilateral parathyroidectomy (97%). Multiglandular disease was present in 16% of the patients, which was identified successfully, by performing intraoperative PTH measurements. The main reasons for not performing a MIP were, neck operations due to prior thyroidectomy and inadequate or conflicting localization or multiglandular disease [18].

## Intra-operative PTH assay

Minimally invasive parathyroidectomy relies on careful preoperative localization procedures to identify the solitary parathyroid adenoma and on intraoperative PTH (IOPTH) monitoring. PTH has a very short half-life of 3-5 minutes [19]. IOPTH monitoring involves sampling of PTH values, preoperative and intra-operatively, and after resection of abnormal parathyroid glands. The definition of a successful parathyroidectomy, utilizing IOPTH data varies by institution. Two common criteria include; a decrease of > 50% from the highest pre-excision value, the Miami criterion, or a decrease of > 50% of the highest pre-excision value, with a return into the normal range of the PTH assay [20-22]. The test often takes up to 30 minutes, which prolongs the operating time, especially in cases in which the PTH level does not fall. Many experienced surgeons get impatient then, because they could perform a bilateral exploration, during the time it took to get the PTH report back. One of the main reasons for Norman et al. to abandon the unilateral parathyroidectomy and the IOPTH measurements [17]. If the 5-minute IOPTH level does not drop 50%, the surgeon must either wait for more IOPTH levels or continue further operative exploration, which can be time consuming [23].

Alheldi et al evaluated 1021 patients, 817 patients with a single adenoma (SA) (83,2%), 99 (10%) with a double adenoma (DA) and 78 (7,6%) with hyperplasia (HA). SA patients exhibited 56, 6 +/- 4,9% decline in IOPTH levels at 5-minutes, compared to 21,3 +/- 4, 5% in DA and 22, 5 +/- 4,3% in the HA Group (p<0,01). Post hoc comparisons revealed, that the 5-minute decrease in the SA group was significantly greater, than either in the DA or HA groups (p<0,01). A 5-minute percentage decline of 35% best distinguished SA from multiglandular disease (85, 3% vs 24, 9%). They concluded, that when IOPTH does not drop at least 35% at 5-minutes post-excision, the surgeon should consider further exploration, rather than waiting for additional IOPTH levels [24]. Other institutions use baseline IOPTH from a peripheral blood sample following anesthesia induction, at adenoma resection (zero value) and 5, 10 and 15 minutes postexcision. A 50% drop in IOPTH levels, with return in the reference range of the IOPTH assay (mostly Nichols Diagnostics Products Corporation, LA, CA or Roche Diagnostics, Indianapolis, IN), is considered a successful parathyroidectomy [19].

## Minimally Invasive Radioguided Parathyroidectomy (MIRP)

MIRP uses a gamma detection probe for identifying parathyroid adenomas during surgery, alone or in combination with IOPTH measurements. Technetium ( $^{99m}\text{Tc}$ ) sestamibi is used as a radiotracer for intraoperative localization of adenomatous parathyroid glands. The injection is usually given 2-3 hours before surgery, because the tracer washes out more quickly from the thyroid than from the parathyroids. Disturbances in parathyroid imaging by thyroid uptake are avoided as much as possible in this way. The lapse of time of time useful to perform surgery is therefore narrow and strict [25]. Several protocols have been developed. Some perform the sestamibi scan on the day of surgery and surgery 3 hours later. Others use a separate day double tracer subtraction scintigraphy protocol, with a low dose injection of the tracer  $^{99m}\text{Tc}$  sestamibi some minutes before the start of the surgery [26,27].

Another method is blocking the uptake of the tracer by the thyroid, through administration of Lugol's solution during 4 days before surgery. On the day of surgery the patient undergoes sestamibi scanning. An ex vivo radioactivity count by the handheld gamma probe of the adenoma 20-40% greater than the value of the background activity is accepted as an identified adenoma. The authors show nice pictures, but do not mention the number of examined patients [28]. Mehrabibahar et al. [29] evaluated 87 patients with previous neck US and MiBi scan, performing radioguided surgery. IOPTH monitoring was not used. One mCi MIBI was injected in the operating room before the beginning of the surgery. MIRP was successfully performed in 86 of 87 patients. The gamma probe was particularly useful in detection of an ectopic parathyroid adenoma in the upper mediastinum. Mean operation time was 24 minutes and the mean hospital stay was 1, 5 day. Radiation exposure was 20 times lower, than using the conventional 20mCi  $^{99m}\text{Tc}$ -MIBI. Frozen section tissue samples for parathyroid adenoma identification were not used. Mean follow-up of 6 months showed no complications or recurrences.

## Frozen section identification in MIP

With the advent of HR-US, sestamibi scanning, IOPTH monitoring and sometimes radioguided parathyroidectomy, identification of parathyroid adenomas and hyperplasia by frozen section tissue samples has become uncommon. Dewan et al. showed in 50 parathyroidectomies, that gross examination was discordant with the frozen section pathology examination in only 3 patients (6%). The decision to omit intraoperative frozen section examination must be balanced against the implications of misdiagnosis and a repeat operative procedure [30].

## CT and MRI in parathyroid imaging

These modalities have no place in the initial evaluation of parathyroid pathology. Both modalities have applications in complex cases, as in the reoperative setting, or in the rare presence of parathyroid carcinoma (1%) [31].

## Complications of MIP and Cost-Effectiveness

In a prospective randomized controlled trial (n=91), unilateral neck exploration yielded the same cure rates and histology as the bilateral approach. However patients in the bilateral group had a higher incidence of early symptomatic hypocalcemia (28% vs 49%), consumed more oral calcium and had lower serum calcium levels postoperatively, compared with the unilateral group. Apart from the reduced risk of hypocalcemia MIP offered a 50% reduction in operating time, a reduced length of hospital stay and a 50% reduction in cost with a mean cost saving of \$ 2693 per patient [15,32]. Udelsman et al. [33] found MIP being superior to conventional parathyroidectomy, based on their results of 1650 consecutive patients with primary hyperparathyroidism. MIP had a cure rate of 99, 4% and a complication rate of 1, 45% vs 97, 1% cure rate and 3, 1% complication rate for conventional, bilateral parathyroidectomy. MIP resulted in a shorter hospital stay and less costs [33].

Karahan et al. [34] evaluated 49 patients with PHP, who underwent MIP under local anesthesia, without any sedation. During MIP gamma probe identification was used for all patients. Of the 49 patients 47 were totally cured. In 2 patients the procedure was switched to conventional bilateral neck exploration. In a UK series of 59 patients with MIP for PHP 53 patients were discharged the same day. Ten percent had an overnight stay for temporary hypocalcemia correction [35]. Bleeding and infection are extremely rare complications in MIP, as is damage to the recurrent laryngeal nerve [35,36]. In contrast to, for example MIVAT intraoperative electrophysiological monitoring of the recurrent laryngeal nerve during MIP is mostly considered as "overdone" [37]. Nevertheless the fear of recurrent laryngeal nerve damage has been the main reason for a shift from the general surgeon to the ENT surgeon as an endocrine neck surgeon.

## Conclusion

In 20 years MIP has been settled definitely, as the procedure of first choice in the surgical management of patients with PHP. It is a safe and efficacious short procedure. Costs, operating time, length of hospital stay and temporary postoperative hypocalcemia are reduced by 50%. Cosmesis is optimal, as is patient satisfaction. MIP can be performed on a day case care under local anesthesia, with or without sedation. Ultrasound, sestamibi scanning, combined with IOPTH measurements or nuclear mapping, result in cure rates of 98-99%. Actually no other complications than postoperative temporary hypocalcemia are seen (10-20%). Bleeding, infection and recurrent laryngeal nerve damage are rare. There is no place for SPECT/CT sestamibi scanning and 3 or 4 dimensional CT or MRI in the initial diagnostic work-up of PHP patients. Exclusion of these modalities from routine parathyroid imaging saves the patient from unnecessary radiation exposure and imaging time. Both general and ENT surgeons can perform MIP safely, with a presumed minimum in the literature of 30 procedures a year. Both MIP and conversion to bilateral neck exploration should be trained.

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