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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

ΘΕΜΑ:

MINIMALLY INVASIVE VIDEO-ASSISTED PARATHYROIDECTOMY (MIVAP) IN THE TREATMENT OF PATIENTS WITH PRIMARY HYPERPARATHYROIDISM: A SYSTEMATIC REVIEW

ΜΕΤΑΠΤΥΧΙΑΚΟΣ ΦΟΙΤΗΤΗΣ:

ΧΟΡΤΗΣ ΠΑΝΑΓΙΩΤΗΣ

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Του Μεταπτυχιακού Φοιτητή Χόρτη Παναγιώτη

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ΑΦΙΕΡΩΣΕΙΣ

Στην οικογένειά μου για την πολύτιμη στήριξη στην εκπόνηση αυτής της Διπλωματικής Εργασίας, καθώς και στους διδάσκοντες, για την επιμόρφωση και καθοδήγηση που παρείχαν σε όλους τους φοιτητές.

ΕΥΧΑΡΙΣΤΙΕΣ

Σε όλους τους διδάσκοντες του Προγράμματος Μεταπτυχιακών Σπουδών για την παρεχόμενη υψηλού επιπέδου εκπαίδευση και τη μεταλαμπάδευση νέων γνώσεων, καθώς και στη Γραμματεία για τη συνεχή στήριξη και καθοδήγηση.

ΠΕΡΙΕΧΟΜΕΝΑ (TABLE OF CONTENTS)

PREFACE

In an era of rapidly evolving knowledge and technological achievements in the field of Medicine and Surgery, a solid tendency to minimise pain and achieve better cosmetic results, while maximising cure rates is being established. Thus, in most surgical specialties, new and constantly improving minimally invasive techniques have become indispensable for the treatment of various conditions. Undoubtedly, one of the most profound examples is laparoscopic cholecystectomy, which is nowadays the gold standard for the treatment of gallstone disease. Lately, new studies have proven the superiority of laparoscopic surgery for the management of various General Surgical conditions, while Robotic Surgery is gradually emerging and redefines surgical frontiers.

Indeed, minimally invasive surgery has revolutionised not only General Surgery (e.g. laparoscopic cholecystectomy, colectomy, Nissen's fundoplication), but also Urology (e.g. robotic radical prostatectomy), Orthopaedics (e.g. arthroscopy), Gynaecology (e.g. laparoscopic hysterectomy), Transplantations (e.g. laparoscopic nephrectomy from a living donor), ENT (e.g. transnasal pituitary adenoma resection) and Cardiothoracic Surgery (e.g. video-assisted thoracoscopic surgery-VATS). It is therefore evident that its importance across a wide spectrum of surgical specialties is considerable, and continuously increasing. The benefits of these techniques, and their promise for reduced postoperative pain, smaller incisions, a more rapid discharge and faster return to normal everyday activities, in conjunction with increased patient satisfaction have rendered them exceptionally appealing.

In this context, minimally invasive techniques have been adopted in Endocrine Surgery in recent years, for the treatment of thyroid, parathyroid and adrenal conditions. An increasing number of papers on laparoscopic adrenalectomy and its indications is being published, while at the same time, thyroid and parathyroid surgeons are implementing techniques that minimise scar length, and offer better cosmetic results. These encompass open techniques with a significantly reduced incision size, but also endoscopic and video-assisted techniques.

With regards to parathyroid gland surgery, one of its strongest indications is primary hyperparathyroidism. For many years, the gold standard for the management of this condition was bilateral neck exploration, with visualisation and investigation of all (in most cases four) parathyroid glands intraoperatively. However, it is well known that in the vast majority of cases, the causative agent for primary hyperparathyroidism is a solitary adenoma in one of the parathyroid glands. Nowadays, modern imaging, and especially the use of cervical ultrasound as well as technetium (99m Tc) sestamibi scan, allows for reliable and successful preoperative identification of the responsible gland in most cases, and thus the need for intraoperative visualisation of the remaining glands has become less evident.

As a result, there has been a gradual shift towards Minimally Invasive Surgery regarding the treatment of primary hyperparathyroidism, and a number of papers from various centers globally acknowledge this as the new gold standard as opposed to bilateral neck exploration for selected cases. The aim of the current systematic review is to assess the role and importance of Minimally Invasive Video-Assisted Parathyroidectomy (MIVAP), in the management of primary hyperparathyroidism. An effort will be made to establish the benefits and limitations of this method compared with traditional bilateral neck exploration. In addition, a comparison between this and other minimally invasive techniques, and primarily open minimally invasive parathyroidectomy, will be attempted, to identify any potential advantages.

An introduction of parathyroid gland anatomy, embryology and physiology will be presented, followed by a description of minimally invasive parathyroid surgical techniques, with special emphasis on MIVAP. Afterwards, by analysing modern global literature and research on this subject, an attempt will be made to assess the significance and potential advantages of MIVAP in the treatment of primary hyperparathyroidism, while identifying and acknowledging its limitations. The results will be valuable not only in the field of Endocrine Surgery, but for all surgeons, as the current review aims to broaden existing knowledge on modern Minimally Invasive Surgery. Hence, new horizons are revealed that aid in the achievement of better cosmetic results, minimisation of pain, and an increase in the quality of care for patients and their satisfaction, which has always been the very essence of the surgical specialty.

INTRODUCTION

Primary hyperparathyroidism (pHPT) is the commonest cause of hypercalcaemia and affects 1-3% of the population in the western world, being the third most common endocrine disorder. Nowadays, an increasing number of patients is being diagnosed with this condition prior to the appearance of symptoms, during routine biochemical screening. Furthermore, it has been acknowledged that surgical management is the only definitive treatment for pHPT, and aims to remove hyperfunctioning parathyroid tissue. Thus far, endocrine surgeons around the world have opted for open bilateral neck exploration (BNE), as the gold standard in the surgical treatment of pHPT. This technique, being exceptionally safe and reliable, allows for direct visualisation of all parathyroid glands, providing the surgeon with the opportunity to assess them and remove the pathological one(s). Nevertheless, traditional parathyroidectomy is correlated with large skin incisions and poor cosmetic outcome, while been accompanied by the disadvantages of an open surgical procedure (pain, increased requirement for analgesia, increased length of hospital stay).

What is more, it has been well recognised that pHPT is caused, in the vast majority of cases, by a solitary parathyroid adenoma (>80%), that secretes excessive amounts of parathyroid hormone (PTH), while the remaining cases are caused by diffuse hyperplasia of the parathyroid glands, multiple adenomas or parathyroid carcinoma (1%). Therefore, it is evident that a targeted surgical approach that would only excise the responsible parathyroid gland, limiting the need for visualisation of the remaining ones, would be highly beneficial for these patients. In this context, minimally invasive parathyroidectomy has gradually established its position in modern surgical practice, and allows for successful resection of the hyperfunctioning gland in most cases. A number of continuously developing minimally invasive procedures have emerged, with the two most popular ones being minimally invasive video-assisted parathyroidectomy (MIVAP) and open minimally invasive parathyroidectomy (OMIP). The former, being the main topic of the current systematic review, requires two predispositions, in order to guarantee successful operative outcome. To start with, accurate pre-operative localisation of the pathological gland is of the essence, in order to selectively target it and avoid the need for visualisation of the remaining glands. For this reason, a variety of imaging modalities exist, that provide reliable and accurate localisation of the hyperfunctioning gland, with the two most widely used being cervical ultrasonography and technetium sestamibi scan. In addition to this, a technique that allows for reliable, intra-operative prediction of the outcome of the procedure is essential, thus ensuring that no pathological tissue is left behind, and in the majority of cases this is achieved by intra-operative PTH level measurement (IOPTH).

Indeed, MIVAP has become increasingly popular in recent years, and together with OMIP, tend to become the new gold standard procedures for selected cases of pHPT.

It is linked with all the advantages associated with minimally invasive surgery, for instance better cosmesis and patient satisfaction, reduced post-operative pain and analgesia requirements, diminished length of hospital stay and a more rapid recovery, while at the same time being at least equally safe and effective as its traditional rival. Moreover, it displays unique features, such as the ability to perform video-assisted bilateral neck exploration, and treatment of concurrent thyroid pathology, that have motivated researchers worldwide to attempt to broaden its indications for the management of this common endocrine condition. However, the relative novelty of minimally invasive parathyroidectomy, together with the fact that no review in literature exists that performs a comprehensive comparison of MIVAP with all other techniques (open BNE and minimally invasive), have generated the necessity for evidence-based recommendations on the suitability of this procedure, its limitations and indications.

As a result, the present systematic review aims to compare MIVAP with open BNE, in an attempt to identify its advantages, drawbacks, and specific disease features where it could be considered superior in the management of pHPT. Furthermore, this review aims to perform an objective comparison of MIVAP with all other minimally invasive procedures for parathyroidectomy, and especially OMIP. All data will be obtained by careful research of existing literature, in order to achieve an objective and structured analysis and comparison among all aforementioned techniques.

In this context, it will be attempted to identify whether an expansion of MIVAP's indications is likely, in order to incorporate a larger variety of patients with pHPT, and even those with secondary hyperparathyroidism. This stems from a number of studies contemplating the use of MIVAP for treatment of patients with multiglandular disease, familial or MEN-associated hyperparathyroidism, inspired by the technique's unique features, and particularly its ability for video-assisted BNE. Out of this research, useful conclusions will be reached, and motivation for future research will be generated.

Initially, this review will present a synopsis of parathyroid anatomy, embryology and physiology, as well as an introduction to primary hyperparathyroidism. Furthermore, it will incorporate a description of minimally invasive techniques for parathyroidectomy, and especially MIVAP, including their indications and drawbacks. In addition to these, an analysis of pre-operative localisation imaging modalities will be presented, together with a report on IOPTH and its role in minimally invasive parathyroidectomy. Moreover, at the core of this review, a systematic analysis of existing literature on MIVAP will ensue, aiming in a comparison of this with traditional, open cervicotomy, as well as with the remaining modern techniques. In the end, it will be attempted to justify whether MIVAP is superior for the treatment of pHPT, and also to delineate specific disease characteristics that could prompt the surgeon to select one technique over the others. As a result, recommendations for current practice and future research will be made.

All in all, MIVAP is a promising and increasingly popular technique for the treatment of this common endocrinopathy, however, as new data continuously become available, an analytical and objective comparison with other techniques, older or contemporary, is of vital importance. The present systematic review aims to serve this role and contribute in steering surgical practice towards a minimally invasive approach, in order to achieve greater patient satisfaction and standards of care. Thus, the foundations of this approach will be solidified by accumulation of existing knowledge and supported by evidence, leading to an era where MIVAP may have a central role in the treatment of primary hyperparathyroidism, beyond the confinements of current guidelines.

PART I

1. PARATHYROID GLANDS

1.1 EMBRYOLOGY OF THE PARATHYROID GLANDS

The parathyroid glands develop between the fifth and twelfth week of gestation. The embryological origin of the superior and inferior parathyroid glands is distinct, which has direct implications in the localisation of the glands, and subsequent surgical management of their conditions.

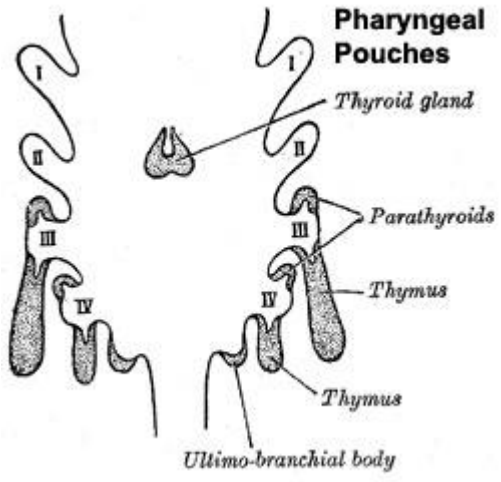


Figure 1: Embryology of the parathyroid glands (Source: https://embryology.med.unsw.edu.au)

The superior parathyroid glands arise from the dorsal endoderm of the fourth branchial pouch, whereas the inferior parathyroid glands arise from the third branchial pouch, along with the thymus gland (Fig.1). The descent of the latter carries the inferior parathyroid glands down with it. In addition, the ventral part of the 4th branchial pouch is fused to the developing thyroid gland, and 90% of superior parathyroid glands remain attached to the thyroid gland in adult life. Moreover, the position of the superior glands tends to be more constant compared to the inferior glands.

All four parathyroid glands move caudally during embryological development, and the multiple ectopic sites in which they may be found is attributable to this migration.

1.2 ANATOMY OF THE PARATHYROID GLANDS

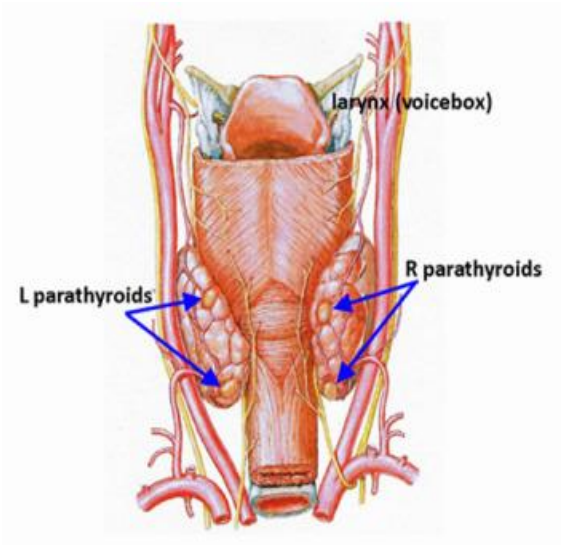
The parathyroid glands were first identified in humans by Ivar Sandstrom, a Swedish medical student back in 1880.

The majority of people have four parathyroid glands (90%), two on either side of the posterior surface of the thyroid gland (Fig.2a). Only a small number of them have three glands (3%), while 7% of the population appear to have more than four glands. The parathyroid glands measure 4mm x 3mm x 2mm and weigh approximately 30-50 mg each. They are brownish-yellow in colour.

The superior parathyroid glands are usually located at the level of the first tracheal ring, where the recurrent laryngeal nerve (RLN) crosses the inferior thyroid artery. On the contrary, the inferior parathyroid glands are, as it has already been stated, more variable in position and are found below the level of the inferior thyroid artery, usually at the inferior lobe of the thyroid gland. In most cases, the superior glands lie posterior and lateral to the RLN, whereas the inferior glands lie anterior and medial to the nerve (Fig. 4). As a result of the migration of the parathyroid glands during embryological development, their location is variable, and for this reason, they may be encountered in a number of ectopic positions, both in the neck and the mediastinum (Fig. 2b).

With regards to the potential ectopic positions, the superior parathyroid glands are more constant in their location, but can be seen anywhere between the thyroid gland and the oesophagus, behind the oesophagus, or in the carotid sheath. What is more, the inferior glands, having a more variable position, may be traced along the inferior thyroid veins, anterior to the trachea, or even in the superior mediastinum, accompanying the thymus. It has been estimated that on average, 15-20% of the population have ectopic glands.

a



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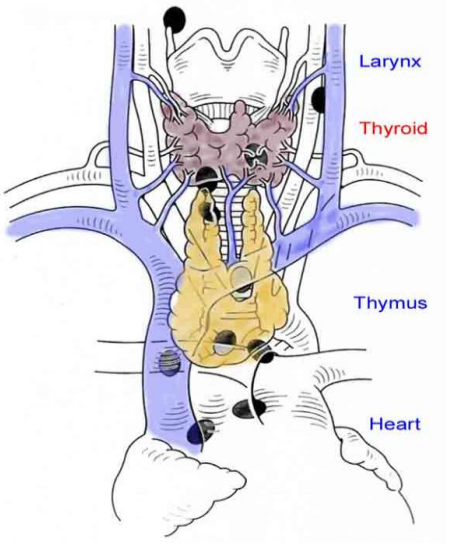


Figure 2a: Usual position of the parathyroid glands Figure 2b: Possible ectopic positions

(Source for both figures: http://www.endocrinesurgery.net.au)

1.3 ARTERIAL SUPPLY TO THE PARATHYROID GLANDS

As a rule, the greatest amount of blood to the parathyroid glands is supplied by the inferior thyroid artery, which is a branch of the thyrocervical trunk, that stems from the subclavian artery. More specifically, the inferior parathyroid glands receive their blood supply almost exclusively from the inferior thyroid artery, and to a lesser extent from the superior thyroid artery. With regards to the superior glands, 80% of cases are

supplied by the inferior thyroid artery (Fig. 3), with the remaining 20% being supplied by the superior thyroid artery, the thyroid ima artery, or aortic oesophageal branches.

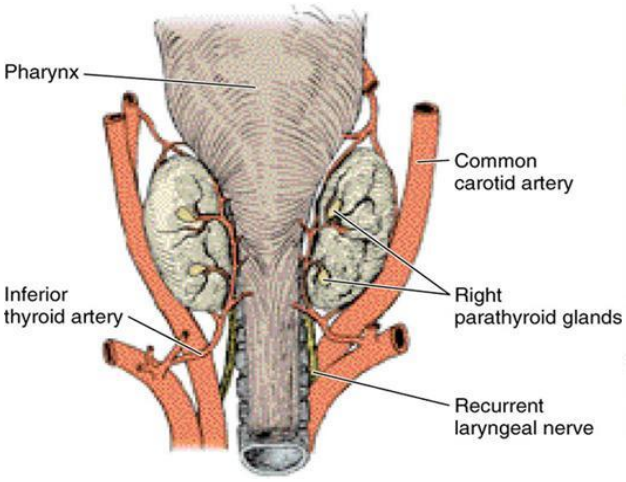


Figure3:Arterial supply to the parathyroid glands

(Source: http://intranet.tdmu.edu.ua)

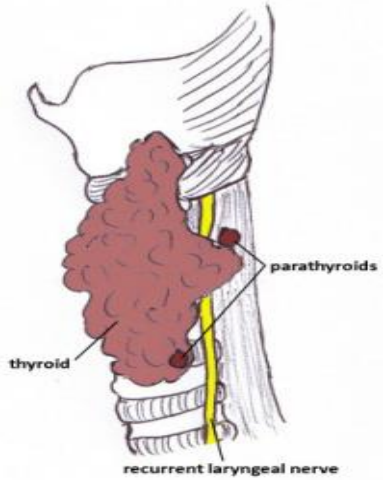


Figure 4: Parathyroid glands and RLN

(Source: http://www.endocrinesurgery.net.au)

1.4 VENOUS DRAINAGE OF THE PARATHYROID GLANDS

The parathyroid glands drain to the venous plexus lying at the anterior surface of the thyroid gland, and then through the superior, middle and inferior thyroid veins drain to the internal jugular and brachiocephalic veins.

1.5 INNERVATION AND LYMPHATIC DRAINAGE OF THE PARATHYROID GLANDS

Innervation of the parathyroid glands is from thyroid branches of the cervical sympathetic ganglia. Lymphatics accompany those of the thyroid gland, and may drain into the anterior cervical nodes (level VI), inferior deep cervical nodes (level IV), or to anterior mediastinal nodes.

1.6 HISTOLOGY

Histologically, the parathyroid glands are comprised of three main types of cells: chief, oxyphil and water-clear cells (Fig. 5). The glands are primarily composed of chief cells and fat, surrounded by a thin fibrous capsule, which also separates the gland into lobules. Chief cells are polygonal cells, containing central round nuclei and granules of parathyroid hormone (PTH). 80% of this type of cells have intracellular fat, and it is the most sensitive cell type to alterations in ionised calcium.

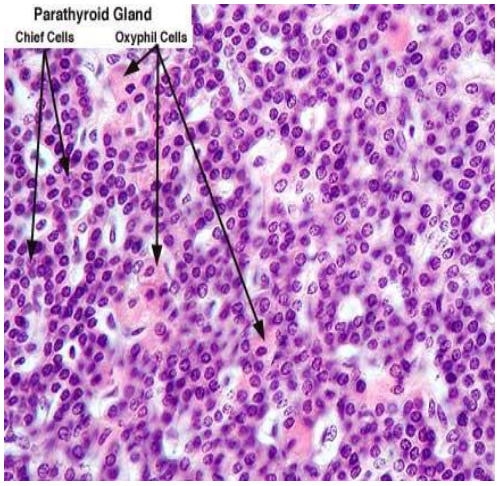


Figure 5: Types of cells within a parathyroid gland
(Source: https://gr.pinterest.com)

The second cell type, oxyphil cells, are slightly larger than chief cells, with their cytoplasm being acidophilic due to the presence of mitochondria. Contrary to their counterparts, they contain no secretory granules. The third type, water-clear cells have a clearly visible cytoplasm, with sharply defined cell membranes.

Apart from the cellular component, the glands contain adipose tissue, which increases with age and obesity, reaching up to 30% of the gland's parenchyma at the age of 25. They also contain fibrovascular stroma, a layer of fibrous tissue. Microscopically, the cells of the parenchyma are arranged in thick branching cords throughout the stroma, with tubular formations also seen in certain cases.

1.7 PHYSIOLOGY

The main function of the parathyroid glands is their unique contribution to calcium homeostasis. Their chief cells secrete parathyroid hormone (PTH), directly into the blood stream. Indeed, PTH along with calcitonin (secreted by parafollicular "C" cells in the thyroid gland) and vitamin D are responsible for maintaining calcium serum levels within normal range. 99% of calcium is in the bones as hydroxyapatite, whereas only 1% is free within the extracellular fluid, and from that, only 40% is in free ionised state, which is the physiologically active form. PTH is a polypeptide containing 84 amino-acids, with three target-organs: kidneys, bones and bowel. It has to be cleaved twice in order to obtain its final active form, it has a half-life of 2-5 minutes, and is degraded in the liver, circulation and kidney.

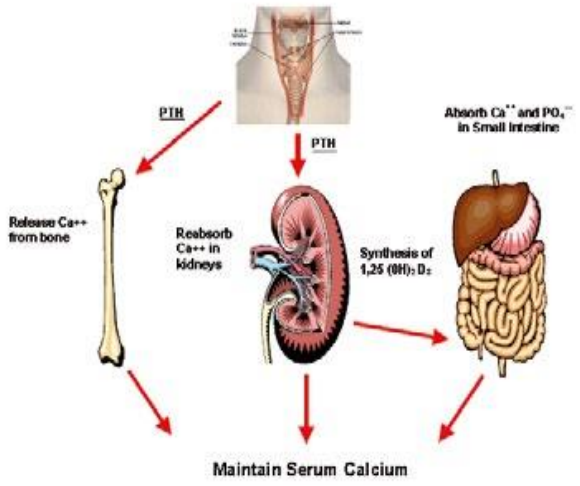


Figure 6: Actions of PTH for calcium homeostasis
(Source: http://sigmadiagnosticsinc.com)

The action of PTH in the kidneys, is to stimulate renal calcium and magnesium resorption, as well as phosphate, sodium and bicarbonate excretion. In particular, calcium is reabsorbed in the ascending loop

of Henle, distal tubule and collecting tubule, while phospahate reabsorption at the proximal convoluted tubule is blocked.

PTH also promotes calcium absorption from bones. This is achieved in two ways. Initially, during the "rapid phase", a rise in serum calcium is achieved within minutes, and occurs by osteoblasts and osteocytes, which mobilise calcium ions from the bone fluid into the extracellular fluid after PTH binds to their receptors. During the second "slow phase", which occurs after a few days, osteoclasts digest formed bone, thus increasing calcium levels in the serum.

Additionally, PTH activates the enzyme 1-hydroxylase which converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D in the proximal convoluted tubules of the kidneys. After its formation, 1,25-dihydroxyvitamin D enhances intestinal absorption of calcium, by aiding the generation of calcium-binding protein within the intestinal mucosal cells. Furthermore, vitamin D provides an additional action for calcium homeostasis, by provoking osteoclast proliferation and bone resorption, in conjunction with PTH (Fig.6).

Biochemically, PTH exerts its action in the cellular level by increasing c-AMP production, which then acts as a second messenger to transmit the signal to the nucleus. The result is an overall increase in serum calcium levels, along with a decrease in serum phosphate level, triggered by reduced calcium. As with every endocrine organ, negative feedback mechanisms also apply for the secretion of PTH by parathyroid glands. This allows the aforementioned glands to decrease the quantity of secreted PTH, once serum calcium levels are back to normal.

2. HYPERPARATHYROIDISM

Three main types of hyperparathyroidism are recognised. Primary hyperparathyroidism is the most common type, and is also the commonest cause of hypercalcaemia at the general population (1). It is characterised by excessive PTH production by the parathyroid glands, which may be a result of a parathyroid adenoma, hyperplasia or carcinoma. In this type, PTH is produced regardless of calcium levels. In secondary hyperparathyroidism, PTH is produced as a response to low serum calcium levels, for instance in renal failure and in malabsorptive conditions. Tertiary hyperparathyroidism is characterised by autonomous excessive secretion of PTH by one of the parathyroid glands, as a result of its hyperplasia owing to secondary hyperparathyroidism. Increased PTH production in this type of hyperparathyroidism continues to occur despite the presence of eucalcaemia, and it may be hard to distinguish from severe secondary hyperparathyroidism.

3. PRIMARY HYPERPARATHYROIDISM

As previously stated, primary hyperparathyroidism (pHPT) is the commonest type of hyperparathyroidism. In the vast majority of cases, it is caused by a solitary adenoma in one of the parathyroid glands (75-85%). In the remaining cases, it may be caused by diffuse parathyroid hyperplasia (10-15%), either in its sporadic type or within the context of Multiple Endocrine Neoplasia (MEN) syndrome (types 1 and 2A), by multiple adenomas (1-3%) or by a parathyroid carcinoma (1%). It appears to have an increasing incidence with age, peaking around the fourth and fifth decade, and it is more prevalent in women (2-3 times) (2, 3). Although initially it was considered a rare condition due to the fact that patients usually presented with advanced symptomatic disease, nowadays it is considered quite common in the developed world, with 1-3% suffering from the condition (4, 5). It has also been found that 2% of post-menopausal women present with symptoms and biochemical findings consistent with primary hyperparathyroidism.

With regards to its causes, pHPT caused by a solitary adenoma usually results in regression of the size of the remaining parathyroid glands, due to excessive calcium levels. When it comes to parathyroid hyperplasia, the majority of cases are sporadic. Nevertheless, 95% of patients affected by MEN 1 syndrome (which encompasses pituitary adenomas, parathyroid hyperplasia and pancreatic islet tumours) typically present with pHPT associated with diffuse four-gland hyperplasia. For MEN 2A syndrome (parathyroid hyperplasia, medullary thyroid carcinoma and phaeochromocytoma), this applies for 5-20% of patients. What is more, multiple adenomas have often been described in patients with MEN 2A syndrome. Finally, parathyroid carcinoma, although consisting a very rare cause of pHPT, may be suspected in cases of profound hypercalcaemia. The lesion is also palpable in 50% of these patients (1).

With its diagnosis being biochemical, primary hyperparathyroidism is characterised by excessive production of PTH by the parathyroid glands secondary to one of the four aforementioned conditions. Total serum calcium is elevated, with an accompanying increase in PTH levels (in a small number of cases there may be normal PTH). In recent classifications, normocalcaemic primary hyperparathyroidism has also been recognised as an entity, which is characterised by elevated PTH levels but normal total and ionised serum calcium levels (2). A number of patients belonging in this last category may in time progress to hypercalcaeimic pHPT.

Several other biochemical findings may accompany the diagnosis of pHPT, such as hypophasphataemia, mild hyperchloraemic metabolic acidosis, raised alkaline phosphatase (ALP) levels and raised 24-hour calcium secretion in urine.

All in all, according to recently published guidelines on the management of primary hyperparathyroidism, serum total calcium, PTH levels, creatinine and 25-hydroxyvitamin D levels should be indispensable components in the biochemical

assessment of a patient with suspected pHPT (2). Additionally, a 24-hour measurement of calcium and creatinine in the urine should be obtained. The reason for this is to diagnose potential familial hypocalciuric hypercalcaemia, which is established in patients with hypercalcaemia, urinary calcium levels <100 mg per 24 hours and a calcium to creatinine clearance ratio <0.01.

Clinical signs and symptoms of a patient with pHPT typically mirror those of hypercalcaemia, which are included in the well-known aphorism of "stones, bones, abdominal groans and psychic moans". Nowadays however, the majority of individuals with pHPT (>80%) are diagnosed in the context of randomly found elevated serum calcium levels and not by symptomatic disease (4). Nevertheless, if symptomatic, a patient may present with a variety of symptoms, which are listed below.

To start with, increased levels of calcium in the urine along with phosphate loss trigger the formation of renal and ureteric stones (15-20%), nephrocalcinosis, polyuria, polydipsia and in advanced cases renal function impairment. Furthermore, patients with pHPT may complain of symptoms arising from their musculoskeletal system, such as pain due to pathological fractures, osteoporosis, bone resorption, or osteoclastoma (brown tumour). Sub-periosteal bone resorption cysts may be seen, particularly in the phalanges and clavicle. Other pPHT – associated bone conditions include osteitits fibrosa cystica, peri-articular calcium deposits, loss of lamina dura around the teeth (pathognomonic), loss of tufts of the terminal phalanx and osteomalacia (if there is additional vitamin D deficiency). An interesting entity which may arise after surgical treatment of pHPT is "hungry bone syndrome". In this case, suppressed PTH levels following surgery and removal of the responsible gland(s), may result in a rapidly established hypocalcaemia, as bones "mop-up" calcium (6). Interestingly, this syndrome may affect up to 25-90% of those with preoperative signs of skeletal disease on radiological imaging, as opposed to 0-6% of hypercalcaemic patients with lack of bone disease prior to surgery.

Hypercalcaemia may also inflict a series of abdominal symptoms. Abdominal pain in these patients may be a result of hypergastrinaemia. Moreover, a number of those affected complain of constipation, nausea, vomiting, weight loss, while others may present with ulceration or even pancreatitis. Neuropsychiatric disorders such as depression, anxiety, confusion, hallucinations, disorientation and dementia may appear in such patients (7).

A minority of patients may present with hypercalcaemic crisis, a medical emergency. Its prevailing symptoms and signs include drowsiness, loss of consciousness/coma, dehydration, weakness, vomiting and renal failure (8). However, when calcium levels are above 15 mg/dl, cardiac implications may arise, such as bradycardia and also peptic ulcer, hypertension and pancreatitis. Such patients should immediately be resuscitated with IV fluids, and be managed with biphosphonates and calcitonin.

Definitive cure of pHPT may only be achieved by surgery, after successful parathyroidectomy (4). In previous years, when nearly all patients presenting with pHPT were symptomatic, surgical management was undoubtedly the preferred course of treatment for all patients. Nevertheless, as in recent years the diagnosis of this condition is often made on the basis of randomly found hypercalcaemia in the absence of any accompanying symptoms, the selection of the appropriate management for this group of patients has been a matter of controversy. Indeed, while parathyroidectomy has unanimously been accepted as standard treatment for symptomatic pHPT (2), researchers have tried to establish which subgroups of asymptomatic patients would benefit from a surgical approach, as opposed to observation or pharmacological therapy.

According to recently published guidelines, parathyroidectomy is strongly indicated when serum calcium is more than 1 mg/dL (or >0.25 mmol/L) above the upper limit of normal (4). In addition, age seems to be a decisive factor, as surgery should be proposed to all patients below the age of fifty. Furthermore, bone mineral density (BMD) is important for the decision-making process. More specifically, as surgery seems to ameliorate BMD and decrease fracture rates, it should be suggested to hyperparathyroid patients with osteoporosis (T-score lower than -2.5 on DXA scan-Dual Energy X-Ray Absorptiometry), fragility fractures, or compression fractures of the vertebrae on imaging of the spine (2). Another crucial factor in favour of surgical management is the presence of renal involvement. Even though nephrocalcinosis and renal function impairment will not improve post-operatively, parathyroidectomy will stabilise glomerular filtration rate (GFR), and prevent the formation of new renal calculi. As such, parathyroidectomy should be offered to all patients with renal calculi on imaging, nephrocalcinosis, hypercalciuria (defined as 24-hour calcium levels in the urine above 400 mg/dL) with increased stone risk, or renal function impairment (GFR < 60 mL/min).

Should a patient meet any of the aforementioned criteria, then surgical treatment should be offered (4). Patients who are diagnosed with pHPT, but do not fall into any of these categories, could be managed conservatively, with close observation and biochemical monitoring once a year (serum calcium and PTH levels), along with measurement of their BMD via DEXA scan at regular intervals. However, in patients who are not able or willing to be observed clinically and biochemically, the need for parathyroidectomy is obvious.

Another group of patients who might benefit from surgical treatment are those suffering from cardiovascular disease. Indeed, pHPT had been accused of augmenting the risk of myocardial infarction, hypertension, stroke, congestive cardiac failure, diabetes and overall mortality in these patients. Thus, surgery could be considered in patients with asymptomatic pHPT and concurrent cardiovascular morbidity, bearing in mind however that there is still conflicting evidence on the improvement of these conditions postoperatively. For instance, an observational study published in 2014 has

failed to demonstrate improvement in a number of conditions, like type 2 diabetes mellitus, hypertension, dislipidaemia and obesity (9).

Parathyroidectomy seems to be more effective and also cost-effective than conservative management for pHPT (2, 4). It is also true that surgery may improve neurocognitive or psychiatric symptoms that originate from this condition, hence improving quality of life for these patients. All in all, even though the benefit of surgery for symptomatic patients is unequivocal, even "asymptomatic" patients should be given the chance to discuss the potential advantages and drawbacks of such an approach with an experienced endocrine surgeon (4).

4. SURGERY FOR PRIMARY HYPERPARATHYROIDISM

4.1 HISTORY

As mentioned earlier, the only definitive treatment for pHPT is parathyroidectomy. The evolution of Surgery with the introduction of minimally invasive techniques has also influenced parathyroidectomy and has shifted surgeons' preference from classic bilateral neck exploration to minimally invasive open or endoscopic modalities.

The first parathyroidectomy was performed by Felix Mandl in Vienna in 1925. One year later, EJ Lewis performed the first parathyroidectomy in the USA. Until very recently, the standard surgical approach has been bilateral neck exploration (BNE), in which the surgeon intraoperatively identifies all four parathyroid glands, and under direct visualisation determines the location and number of the pathological ones (e.g. adenoma, double adenoma, hyperplasia).

The first step to the path of "minimally invasive parathyroidectomy (MIP)" was endeavoured by Tibblin in 1982, who performed unilateral neck exploration for pHPT. In 1983, Adinolfi attempts a mediastinal endoscopic technique for parathyroidectomy, followed by a thoracoscopic technique by Prinz in 1994, in order to excise enlarged mediastinal parathyroid glands.

MIP was allowed to flourish as it was recognised that pHPT is caused in the majority of cases (reaching 85%) by a solitary parathyroid adenoma. The development of new imaging modalities (especially sestamibi scintigraphy) that allowed reliable pre-operative recognition of the responsible gland (alone or in conjunction with cervical ultrasonography), as well as the endorsement of intra-operative PTH levels (IOPTH) measurement were the two determining factors for the global acceptance of these techniques. IOPTH measurement and more specifically, a >50% drop in PTH ten minutes after removal of the responsible parathyroid gland, is a very reliable confirmation of the successful outcome of the operation and reassures the surgeon that no diseased gland has been left behind (e.g. in cases of multiple adenomas or diffuse

hyperplasia). As such, the introduction of sestamibi scan in 1992 and IOPTH in 1996 are considered the milestones of MIP evolution.

In 1996, Gagner performs the first endoscopic parathyroidectomy (10). This was followed a year later, by the introduction of Minimally Invasive Video-Assisted Parathyroidectomy (MIVAP) by Miccoli (11, 12). During the same year, Norman and Cheda described minimally invasive radio-guided parathyroidectomy (MIRP), which required a hand-held gamma probe to lead the surgeon to the responsible adenoma (13). Two years later, in 1999, Henry reports his results with minimally invasive videoscopic parathyroidectomy by lateral approach, during which an incision is made on the anterior border of the sternocleidomastoid muscle, and by using carbon dioxide insufflation, the hyperfunctioning gland is successfully recognised and removed (14). This was followed by focused parathyroidectomy using a lateral incision, performed in 2000 by Udelsman (15).

A description of the main MIP techniques will be attempted, emphasising on MIVAP, which is the procedure of interest in this systematic review.

4.2 MINIMALLY INVASIVE VIDEO-ASSISTED PARATHYROIDECTOMY (MIVAP)

Minimally invasive video-assisted parathyroidectomy (MIVAP) was initially introduced by Miccoli in 1997, and is considered as one of the most popular minimally invasive techniques for parathyroidectomy for pHPT. Although data is often conflicting, there is evidence that MIVAP has certain advantages over both open minimally invasive parathyroidectomy (OMIP) as well as other endoscopic techniques (16). MIVAP is performed either under general or loco-regional anaesthesia, by means of a cervical block. The patient is placed in the supine position and the neck is slightly extended. The standard approach includes a surgeon and two assistants, one holding the endoscope, and the other holding the retractors.

Figure 7: Minimally invasive video-assisted parathyroidectomy (MIVAP)
(Source: http://www.endocrinesurgery.net.au)

The skin incision is much smaller than in BNE, with its length varying between 1.5 and 2 cm. It usually lies in the midline, between the cricoid cartilage and the sternal notch and its exact position is occasionally influenced by pre-operative imaging findings (16). The next step is to successfully separate the thyroid lobe from strap muscles, and this is accomplished

by Farabeuf retractors, held by the surgeon's assistant. The thyroid lobe is retracted medially and the strap muscles are retracted laterally. After creating a satisfactory operative space, the endoscope is inserted (5mm, 30 degrees), held in place by the second assistant, together with the surgical instruments through the incision. In MIVAP, no trocars are used, and what is more, no gas insufflation is necessary. The absence of trocars in this operation renders the assistant capable of moving the endoscope more freely, and this consists one of MIVAP's advantages over other endoscopic techniques (Fig.7).

After completely separating the thyroid lobe from the strap muscles, and identifying the recurrent laryngeal nerve (RLN) on the respective side, the surgeon attempts to identify the pathological parathyroid gland in the anatomical position suggested by the pre-operative imaging modalities (especially cervical ultrasound and /or sestamibi scan). Furthermore, MIVAP offers the opportunity for visualisation and assessment of the remaining parathyroid glands (on the same or the contralateral side) through the same incision. This might be required in cases of multiglandular disease suspicion. That could be suspected if PTH fails to drop to a satisfactory level intra-operatively, thus implying residual hyperfunctioning parathyroid tissue. Additionally, double ipsilateral glandular enlargement seen during the operation could obviate the need for bilateral exploration, which may be achieved by MIVAP. Moreover, inadequate or conflicting localisation of the hyperfunctioning tissue during the pre-operative period could necessitate visualisation of all four glands. The opportunity for bilateral exploration by MIVAP, similar to BNE, is one of the most crucial advantages of this approach in comparison to other MIP techniques (17).

After recognition of the responsible gland, it is bluntly dissected with spatulas and its vascular pedicle is subsequently clipped with titanium clips or ligated. Once the pedicle is removed, the gland can be removed via the skin incision. IOPTH measurement will then either confirm the successful outcome of parathyroidectomy, or dictate the need for further cervical exploration.

4.3 VIDEO-ASSISTED PARATHYROIDECTOMY BY THE LATERAL APPROACH (VAPLA)

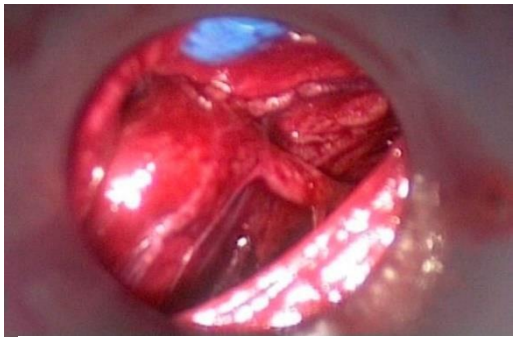


Figure 8: Exposure during VAPLA (Source: http://www.elsevier.es)

This technique was introduced by Henry in 1999. As implied by its name, a lateral incision of approximately 12mm is made on the anterior border of the sternocleidomastoid muscle (SCM), 3-4cm above the sternal notch (18). After careful dissection, the pre-vertebral fascia is reached. This is followed by insertion of two 2.5mm trocars along the anterior border of the SCM, 3-4cm above

and below the line of the original incision. Through the latter, the endoscope trocar is inserted (10mm ,0 degrees). Insufflation with carbon dioxide is used at 8 mmHg, and video-assisted exploration of the parathyroid glands on this side ensues. Once the pathological gland is identified, the vascular pedicle is ligated and cut, and the gland is free to be removed (Fig. 8). In cases of small adenomas, their removal is completed through the 10mm trocar, however for large adenomas that cannot fit through the trocar, the latter is removed and then the gland is extracted from the trocar site under direct vision (16). It would be worth noting that during the original VAPLA technique as it was described by Henry in 1999, the trocars were removed immediately after visualisation of the responsible gland, and then the adenoma was ligated and removed through the skin incision (14). In addition, VAPLA can only achieve unilateral cervical exploration, and does not allow the surgeon to visualise the contralateral glands if required during the operation.

4.4 MINIMALLY INVASIVE RADIO-GUIDED PARATHYROIDECTOMY (MIRP)

In 1996, Norman and Cheda described minimally invasive radio-guided parathyroidectomy (MIRP). In this technique, the surgeon holds a gamma probe, which enables him to identify and dissect the responsible parathyroid gland, as well as intra-operatively confirm the successful removal of all hyperfunctioning tissue. Two to four hours before the procedure, technetium-99m sestamibi is administered to the patient intravenously. A transverse, 2.5-4cm incision is made at about 2cm above the sternal notch (13). The strap muscles are separated in the midline and then carefully dissected. Scanning of the neck with the gamma probe follows, with subsequent exploration of the area with the highest measurements. Once the adenoma is ligated and removed, its radioactivity is measured ex vivo and then compared to that acquired by a slow motion of the probe over the thyroid gland (Fig. 9). The suspected removed parathyroid adenoma's radioactivity concentration has to exceed 20% of background radioactivity levels (13). One of the most important advantages of MIRP is that IOPTH measurement for confirmation of the operation's successful outcome is not necessary, thus reducing operative time overall. On the other hand, this technique requires coordination among various teams, especially between the surgeon and the Nuclear Medicine department.

Figure 9: Minimally invasive radio-guided parathyroidectomy (MIRP)
(Source: https://www.slideshare.net)

All in all, although MIRP is still part of the armoury for pHPT, it is not as popular as its counterparts (16).

4.5 ENDOSCOPIC PARATHYROIDECTOMY (EP)

Introduced by Gagner in 1996, endoscopic parathyroidectomy (EP) involves the use of a central trocar, through which a 5mm endoscope is inserted, as well as two or three other trocars for instrument insertion and manipulation. The procedure requires gas insufflation to create a working space. After carefully dissecting below the platysma and separating the strap muscles in the midline, the surgeon dissects the thyroid lobe from the fascia to visualise the parathyroid glands (Fig. 10). In recent years, EP has also been performed by extracervical routes, in which access to the glands has been obtained from the chest wall, the breast or the axilla (16). What is more, instead of using carbon dioxide insufflation, many surgeons employed mechanical external retraction. This change occurred as central approach with gas insufflation does not facilitate visualisation of posteriorly located parathyroid adenomas (12). For such lesions, lateral access using the space between the strap muscles and the carotid sheath could be employed. These techniques, although guaranteeing better cosmetic results, are more challenging to perform, require lengthier dissection and induce more significant tissue trauma, in addition to increasing operative time.

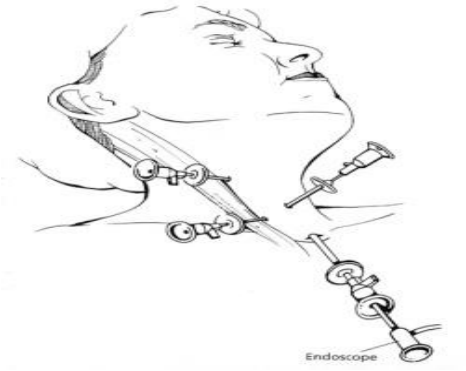


Figure 10: Endoscopic parathyroidectomy (EP) (Source: http://www.endocrinesurgery.net.au)

4.6 OPEN MINIMALLY INVASIVE PARATHYROIDECTOMY (OMIP)

Figure 11: Open minimally invasive parathyroidectomy (OMIP) (Source: https://www.uclahealth.org)

Open minimally invasive parathyroidectomy (OMIP) is the most popular and preferred minimally invasive technique by endocrine surgeons (16). Either a central or a lateral (over the anterior border of SCM) incision is made, measuring 2.5-5cm (or even smaller in certain centres), and a focused parathyroidectomy then takes place, based on pre-operative imaging. With regards to selection of the appropriate

approach, central or lateral, the former allows visualisation of practically all localised inferior parathyroid glands, as well as a number of superior glands that do not lie in ectopic sites (19). Lateral approach is preferred for re-operative cases, as well as for superior glands that lie deeply or laterally (19). After making the incision and reaching the strap muscles, the latter are dissected and lateralised. The thyroid lobe is retracted medially after careful mobilisation. After ensuring a satisfactory working space between the thyroid lobe and the carotid sheath, the RLN is identified and preserved. After successful identification of the diseased gland, its vascular pedicle is clipped or ligated and the gland is cautiously extracted, with care not to break its capsule, thus avoiding parathyromatosis (Fig. 11). After removal of the excised parathyroid gland, measurement of IOPTH follows to determine the outcome of the operation. This technique has a relatively steep learning curve and is reproducible. On the other hand, due to absence of endoscopic assistance and image magnification, the anatomical structures related to the operation are not seen as clearly as they are depicted with the aforementioned MIP modalities. Furthermore, as a rule, OMIP requires a longer incision than the other techniques.

5. INDICATIONS FOR MINIMALLY INVASIVE PARATHYROID SURGERY

For many decades, the gold standard for the treatment of pHPT worldwide has been bilateral neck exploration (BNE). The cure rate achieved by BNE exceeds 95%, with only minor morbidity rates, which do not exceed 3%. (16). Nevertheless, due to its invasiveness, the length of its incision with profound cosmetic implications as well as the requirement for longer hospital stay, minimally invasive techniques gradually emerged and constantly demonstrate their significance for the present and future of Endocrine Surgery. This was allowed by the conclusion that in the majority of cases (approximately 85%), pHPT is caused by a single parathyroid adenoma (2, 16, 19). Given this fact, precise and reliable pre-operative localisation of the responsible gland would enable the surgeon to specifically target the lesion through a smaller incision, avoiding unnecessary dissection and potential trauma to the remaining healthy parathyroid glands or other important cervical structures, such as the RLNs. In order for such a shift to occur, these modern techniques had to prove equally effective and safe. In addition, since these techniques do not involve visualisation of all parathyroid glands, as is the case in BNE, accurate pre-operative localisation imaging modalities should be established, and also a way to intra-operatively ascertain that the outcome of the operation is successful, with no residual pathological tissue left behind. Accurate and reliable pre-operative localisation of the pathologically enlarged parathyroid gland(s) is achieved primarily by cervical ultrasonography and 99-Technetium sestamibi scan. As for the confirmation of removal of all hyperfunctioning parathyroid tissue, this is made by intra-operative PTH measurement (IOPTH), which should drop by more than 50% within 15 minutes following parathyroidectomy.

To start with, candidates for minimally invasive parathyroidectomy should be sought among those with symptomatic pHPT, or asymptomatic disease fulfilling the criteria which were outlined in a previous part of this review. According to recent guidelines introduced by the American Association of Endocrine Surgeons, minimally invasive techniques should be employed in cases where a solitary parathyroid adenoma is identified and adequately localised on pre-operative imaging (2). Based on the same guidelines, MIP should not be suggested for patients with suspected or already known multiglandular disease. What is more, if multiglandular involvement is found during MIP, this should prompt the surgeon to proceed to BNE. BNE should also be attempted if the surgeon fails to identify the pathological gland, or if IOPTH levels do not drop satisfactorily after ligation and removal of the gland (2).

An important consideration is that MIP can also apply for patients with persistent or recurrent hyperparathyroidism (19). On the other hand, negative or absent pre-operative imaging for localisation of the adenoma, or else contradictory findings on two imaging modalities should deter the surgeon from attempting MIP.

An important consideration is the fact that MIVAP is a technique that allows video-assisted bilateral neck exploration, with potential visualisation of all parathyroid glands, thus limiting the need for conversion to open BNE. This is facilitated by the central incision made for MIVAP, and external retraction (20). Furthermore, IOPTH measurement could be avoided in cases of MIVAP-assisted BNE. Indeed, as found in a randomised clinical trial by Miccoli et al (22), BNE can be performed endoscopically without concurrent IOPTH measurement with equal effectiveness, saving operative time and reducing cost. The only drawback found in this trial was that occasionally this technique resulted in unnecessary excision of glands that were enlarged, but not pathological (19, 22). The opportunity for video-assisted BNE, achieved by MIVAP, could potentially convince surgeons to prefer minimally invasive techniques over open BNE even for cases with suspected multiglandular disease and discordant pre-operative imaging findings, or even for patients with familial primary hyperparathyroidism (16).

What is more, MIVAP as well as OMIP allow for regional or even local anaesthesia, providing an appealing alternative to general anaesthesia (GA). In this context, MIVAP under regional anaesthesia (by means of a bilateral deep cervical block) has been demonstrated as being equally effective to MIVAP under GA, requiring less operative time and post-operative analgesia (21). Similarly, OMIP may be performed under loco-regional or even local anaesthesia, providing significant advantages for the patient (7). As a consequence, parathyroidectomy may now be considered even for groups of patients who were unfit for surgery under GA, for instance the elderly or individuals with concomitant severe co-morbidities. Such individuals used to be managed conservatively with pharmacological treatment, but in the era of minimally-invasive parathyroidectomy, surgery might also be considered for them.

6. CONTRAINDICATIONS FOR MINIMALLY INVASIVE PARATHYROID SURGERY

In general, parathyroidectomy, minimally-invasive or not, is contraindicated for patients who are considered high-risk for surgery (although as stated above, the performance of certain MIP techniques under loco-regional anaesthesia provides an opportunity even for such patients to be surgically treated). In terms of contraindications for minimally-invasive parathyroidectomy, these may be broadly divided into absolute and relative.

In the first category, one of the contraindications is discordance between pre-operative localisation imaging modalities (2, 19). Indeed, the suspicion of multiglandular disease hinders the performance of MIP. Of course, as already mentioned, this may not be the case for modalities like MIVAP, which allow for bilateral neck exploration endoscopically. Nevertheless, this is still not incorporated in the latest guidelines, and as such, MIP is not recommended for suspected multiglandular disease (2). A group of patients that have a strong likelihood to present with multiglandular disease are those affected by Multiple Endocrine Neoplasia (MEN) syndromes, and in particular types 1 and 2A. As a result, patients with MEN syndromes are not ideal candidates for MIP.

Moreover, patients suffering from parathyroid carcinoma will most likely require an extensive, oncological operation, in which the ipsilateral thyroid lobe as well as the strap muscles on the lesion's side will need to be excised (4). It is evident that such delicate and extensive tissue excision will not be facilitated through a small skin incision and restricted visual field, and thus MIP is not routinely recommended for such patients (19). Furthermore, previous cervical irradiation is considered an absolute contraindication for modern techniques, as it increases the risk of identification of thyroid malignancy. Concurrent thyroid pathology necessitating surgical management is also considered to be a contraindication for MIP, although MIVAP may allow simultaneous management of both conditions, and even achieve bilateral thyroid lobe resection (16).

Apart from these, there are also a few relative contraindications. These include previous neck surgery, which would increase the potential to damage important cervical structures, notably the RLN. Similarly, known injury to the contralateral RLN dissuades a surgeon from attempting MIP. What is more, patients under anticoagulation therapy or suffering from chronic renal failure are not ideal candidates for modern parathyroidectomy techniques and a conventional approach should be preferred for them (19). This is also the case for morbidly obese patients.

Of course, these contraindications are being tested in a number of studies, and they are prone to modification. Indeed, according to a retrospective review published in 2010, previous head and neck irradiation should not be considered an absolute contraindication for MIP, provided that a single parathyroid adenoma has been

identified in pre-operative imaging and thyroid malignancy has already been excluded (23). As already mentioned, this applies for a number of other so far termed "contraindications", like the presence of multiglandular disease or concomitant thyroid pathology, for which MIVAP above all other minimally-invasive techniques seems to be a reliable alternative. It is profound that further studies need to be performed in order to further clarify such issues and provide guidelines for future practice.

7. PRE-OPERATIVE LOCALISATION IMAGING MODALITIES

The importance of pre-operative imaging for localisation of pathological parathyroid gland(s) has already been stressed. Minimally-invasive parathyroid surgery is currently indicated for cases of solitary parathyroid adenomas, and in order for them to be confirmed and successfully localised, imaging modalities are of the essence. Such modalities also provide the surgeon with valuable information concerning the gland's relationship with adjacent anatomical structures, primarily the thyroid gland. However, an important fact that needs to be highlighted, is that pre-operative imaging modalities have no role in the diagnosis or exclusion of pHPT (2, 19). They should be performed only after a decision for surgical management has been made, in order to guide the surgeon and determine the type of surgical approach (conventional or focused). In this context, negative pre-operative imaging does not exclude a patient from being a candidate for parathyroidectomy. What is more, patients with initially negative imaging findings who had further tests in high-volume centers, eventually had successful localisation of their disease with sensitivity reaching 92% (2). Consequently, it is evident that even patients with negative or contradictory findings on pre-operative imaging should be referred to an endocrine surgeon for further management. Another important point for consideration, is that imaging accuracy in cases of multiglandular disease drops significantly.

Imaging modalities can be non-invasive or invasive. The first category includes cervical ultrasonography, nuclear medicine (sestamibi technetium-99 scintigraphy, usually with single-photon emission computed tomography-SPECT), 4-dimensional computed tomography (4D-CT) and magnetic resonance imaging (MRI) (4, 19). In the majority of cases, an ultrasound and a sestamibi scan, either alone or in conjunction are employed for pre-operative localisation of the enlarged gland(s). In terms of invasive modalities, these include selective venous sampling, selective arteriography and fine needle aspiration (FNA) biopsy.

8. NON-INVASIVE MODALITIES

8.1 CERVICAL ULTRASONOGRAPHY

Being the least invasive and expensive of all pre-operative imaging modalities, high-resolution cervical ultrasound is easily accessible and requires no radiation. A high-

frequency linear transducer is used, ranging from 12 to 15 mHz (19). This modality is very reliable for detection of parathyroid adenomas, with its sensitivity being 27-95% and its specificity reaching up to 92-97%. This reported variation in sensitivity rates is due to the fact that detection of pathological tissue by ultrasound is at a great extent dependent on the operator. Parathyroid glands are seen as solid nodules, hypoechoic, that are well-circumscribed and oval-shaped.

Apart from operator experience and skill, a number of other factors diminish the reliability of ultrasound imaging (19). To start with, patient obesity impedes adequate visualisation of parathyroid glands. Furthermore, simultaneous thyroid disease, for instance multinodular goitre and thyroiditis, is another contributing factor, decreasing US sensitivity to 47-84% (3). The same applies for recurrent disease or patients with a previous cervical operation. In terms of glandular size or location, smaller glands or those found in the mediastinum, retrotracheal or retroesophageal space are harder to trace by ultrasonic imaging. In addition, multiglandular disease may hamper the radiologist. Other factors that may reduce US sensitivity are: prominent blood vessels, cervical lymph nodes and longus colli muscle (3).

As a rule, normal parathyroid glands cannot be distinguished sonographically, due to their small size and acoustic resemblance with regards to neighbouring thyroid tissue (3). However, pathological parathyroid tissue is hypoechoic relative to the thyroid lobe and thus may be localised. In the case of adenomas, these are well-circumscribed lesions, longitudinal, solid and hypoechoic (Fig.12).

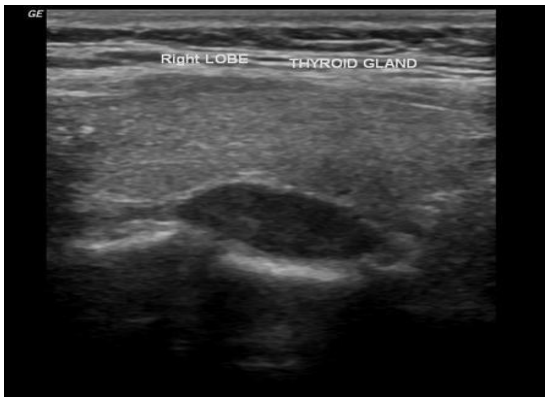


Figure 12: Parathyroid adenoma
(Source: https://radiopaedia.org)

The possibility of an intrathyroidal parathyroid adenoma should not be overlooked. This might occur in 5% of cases, and its confirmation may require ultrasound (US)-guided fine needle aspiration (FNA). The latter might also be used in cases of persistent or recurrent disease. Indeed, PTH washout concentration from the aspirate may imply parathyroid pathology, thus allowing the surgeon to perform MIP even with negative cytology in cases of recurrent or persistent disease. Nevertheless, US guided FNA is seldom required for parathyroid lesions, and might have untoward effects (2). Hence, FNA should only be reserved for difficult cases and under no circumstances should it be performed when suspicion of parathyroid carcinoma exists.

8.2 TECHNETIUM (Tc-99m) SESTAMIBI SCAN

The second most prominent pre-operative localisation modality for pHPT is sestamibi scan (technetium-99m-methoxyisobutyl isonitrile). Displaying a selective affinity for

pathological parathyroid glands, sestamibi has now become the agent of choice for localisation of parathyroid lesions with nuclear medicine (3). Two methods aim to distinguish the drug's uptake by hyperfunctioning parathyroid tissue from that by the normal thyroid gland. In the first method, sestamibi is used in a dual radionuclide approach with subtraction imaging (with I-123 or Tc-99m pertechnate). In the latter, sestamibi is used on its own, in a dual phase study (early and delayed).

As far as dual radionuclide approach is concerned, sestamibi is administered as a thyroid-parathyroid agent, however subtraction imaging requires simultaneous administration of an additional thyroid imaging agent, which is I-123 or Tc-99m. Digital subtraction of the thyroid images from the sestamibi images ensues, with the residual signal representing parathyroid uptake. The reliability of Tc-99m-sestamibi for imaging of parathyroid glands is influenced by a number of factors, such as regional perfusion, parathyroid gland dimensions and functional status, cell cycle phase as well as the presence of cells rich in mitochondria (3).

When it comes to the second method, the so-called "dual phase technique", its foundation is grounded on the fact that parathyroid adenomas retain sestamibi for longer than the thyroid gland (1-3 hours after administration of the agent). Thus, a differential washout of sestamibi is created between the thyroid gland and enlarged parathyroid(s). The first set of images is taken after injection of sestamibi (early phase), and the second is obtained two hours later (delayed phase) (Fig.13). Parathyroid tissue is richer in mitochondria and keeps sestamibi inside the cells.

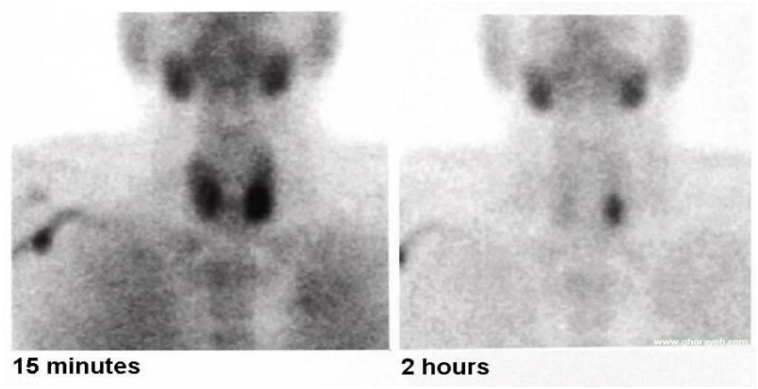


Figure 13: Sestamibi scan: early and delayed phase (Source: http://www.ghorayeb.com)

If a comparison of both methods for sestamibi scintigraphy was to be made, dual phase techinique is much simpler and requires no cervical immobilisation, which is a prerequisite for double-tracer sestamibi. On the other hand, one of its drawbacks is that concurrent thyroid pathology, for instance hyperplastic nodules, chronic thyroiditis, thyroid adenomas and Hurthle cell lesions may lead to false positive results, as they retain sestamibi longer than normal thyroid parenchyma. In such cases, the use of subtraction techniques may provide valuable additional information.

Overall, sestamibi scintigraphy is very accurate for pre-operative localisation of parathyroid adenomas, with its sensitivity ranging from 54% to 100%, and in most studies from 80% to 90% (3). Its sensitivity and specificity may be further enhanced by adding single photon emission computed tomography (SPECT), which may more

accurately distinguish focal Tc-99m-sestamibi retention by thyroid nodules and parathyroid glands. Additionally, this modality may trace ectopic adenomas more accurately, for instance those found in the mediastinum. Furthermore, sestamibi can be combined with other anatomical imaging modalities, such as US, CT or MRI. The use of SPECT/CT for patients with previously untreated pHPT has been studied, with discordant results, as some demonstrate an improvement in sensitivity and positive predictive value, while others fail to trace such benefit (3, 24). Nevertheless, it is reportedly beneficial for identifying ectopic parathyroid glands.

An important point that needs to be stressed is that the combination of cervical ultrasonography and sestamibi is superior to each of them being used separately. Indeed, their combination improves sensitivity and accuracy in pre-operative localisation of abnormal parathyroid tissue (2). Sensitivity may reach 96%, with satisfactory specificity (83%) and positive and negative predictive values (88% and 94% respectively) (25). Such findings are confirmed by a number of studies, which show that sensitivity ranges from 78-96% when these modalities are combined.

8.3 COMPUTED TOMOGRAPHY (CT)

Computed tomography (CT) is another modality that may assist the surgeon in pre-operative localisation of enlarged pathological glands. The use of CT for this purpose is grounded on the vascularity of the parathyroid glands and their enhancement after administration of intravenous (IV) contrast (3). This method's sensitivity ranges from 40% to 86%, and this variation is due to the technique itself as well as the radiologist's experience. The accuracy of CT may be further diminished for parathyroid glands located in the mediastinum or the sternal notch, as they may be mistaken for lymph nodes. Obviously, localisation of pathological parathyroid tissue by CT is not indicated in patients who are unable to receive IV contrast (chronic renal failure or allergy). In addition, due to exposure of the thyroid gland to radiation, it should be used with caution in patients younger than 30 years old (4). This modality may provide valuable information in cases of inconclusive or discordant results by ultrasound and sestamibi, as well as for localisation of ectopic glands.

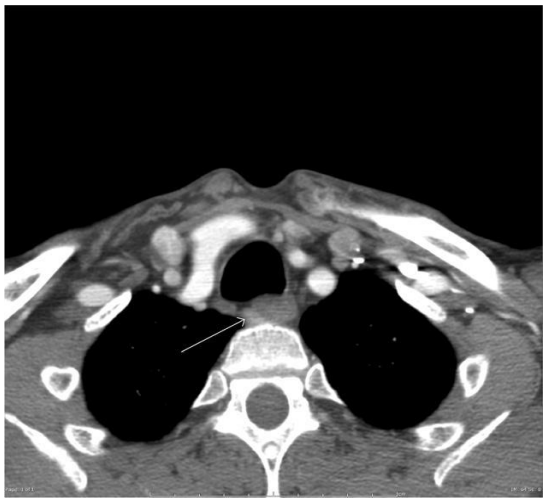


Figure 14: CT image of an ectopic parathyroid adenoma (arrow)
(Source: https://radiopaedia.org)

While conventional CT scanning provides little utility, its major contribution to parathyroid localisation came after the evolution of four-dimensional (4D) CT. The

latter is able to trace changes in the perfusion of contrast over time, along with displaying three dimensional anatomical CT images (Fig.14). In other words, apart from obtaining classical anatomical CT images, the surgeon may now obtain functional information as well. This happens as fast uptake and washout of IV contrast from pathological parathyroid tissue occurs. In a study published by Rogers et al in 2006 (26), 4D-CT not only superseded sestamibi and ultrasonography in terms of sensitivity (88% versus 65% and 57% respectively) when attempting to localise the side of the cervix in which pathological glands lie (left or right), but also when tracing the precise quadrant of the glands' location within the neck (70% versus 33% and 29% respectively). These findings were of particular importance for cases of reoperation.

Such findings were confirmed in another study by Starker et al (27), which also showed that 4D-CT is more sensitive than sestamibi and ultrasound (93.9% versus 61.5% and 71.2% respectively) for correctly lateralising pathological parathyroid tissue to one side of the neck, as well as for identifying the correct quadrant of their position (85.7% versus 40.4% and 48% respectively). In addition, this study showed that 4D-CT is by far superior to the other two imaging techniques in terms of prediction of multiglandular disease, which reached 85.7%. All in all, 4D-CT is a reliable and valuable adjunct to pre-operative planning for MIP, however its use should be judicious due to ionising radiation.

8.4 MAGNETIC RESONANCE IMAGING (MRI)

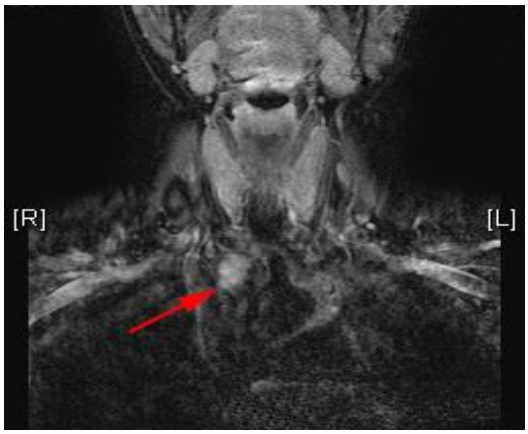


Figure 15: MRI scan with parathyroid adenoma identified low in the neck (Source: http://www.endocrinesurgery.net.au)

MRI is another tool in the pre-operative parathyroid gland localisation strategy. Parathyroid adenomas usually display low intensity on T1-weighted images and high intensity on T2-weighted images, being isointense relative to neighbouring muscular tissue. However, abnormal parathyroid glands enhance significantly after administration of paramagnetic contrast intravenously (gadolinium) on T1-weighted images (Fig.15). As MRI has no ionising radiation, it is frequently preferred over CT. The sensitivity of MRI for localisation of hyperfunctioning parathyroid glands reaches 69%-88%, while its false positive results range between 1.6% and 10%, primarily in cases of concurrent thyroid pathology and cervical lymphadenopathy (3). What is more, MRI has been shown to be more sensitive than sestamibi and ultrasound in cases of persistent or recurrent hyperparathyroidism (88% versus 80% and 58% respectively) (28), although the difference between MRI and sestamibi was not statistically significant. The

combination of MRI and sestamibi demonstrated an even increased accuracy (92%). In another study by Munk et al (29), MRI was successfully employed in cases of discordant sonographic and sestamibi findings. When MRI was in accordance with either US or sestamibi, accurate localisation was achieved at all times.

9. INVASIVE MODALITIES

Invasive modalities are reserved for cases of laborious pre-operative localisation of the pathological parathyroid glands, when non-invasive techniques are inconclusive. Such methods include selective venous sampling (SVS) and selective angiography. SVS and subsequent measurement of a venous PTH gradient aim for identification of pathological parathyroid tissue (lateralisation). A 1.5 to 2-fold increase in PTH levels taken from certain cervical vein drainage locations compared to a peripheral location is judged as an abnormal elevation. Samples may be taken from a variety of veins, including superior thyroid, internal jugular, innominate, inferior thyroid, thymic, left superior intercoastal, superior vena cava (above and below azygos vein), right hepatic, inferior vena cava and both iliac veins. Sensitivity of selective venous sampling may reach 93% in cases of negative, discordant or inconclusive non-invasive imaging, reaching 100% for parathyroid glands with mediastinal position (30). For recurrent or persistent hyperparathyroidism, sensitivity may reach 89%, hence providing effective localisation of pathological tissue (31). As far as selective arteriography is concerned, this can be obtained through combination of selective trans-arterial hypocalcaemic stimulation with non-selective venous sampling. Sodium citrate is initially injected to induce hypocalcaemia, subsequently followed by baseline and timed superior vena cava samplings while arteriography concurrently takes place. A positive localisation outcome is reached if PTH is increased to 1.4 times the baseline or alternatively if a blush is noticed on arteriography (Fig.16).

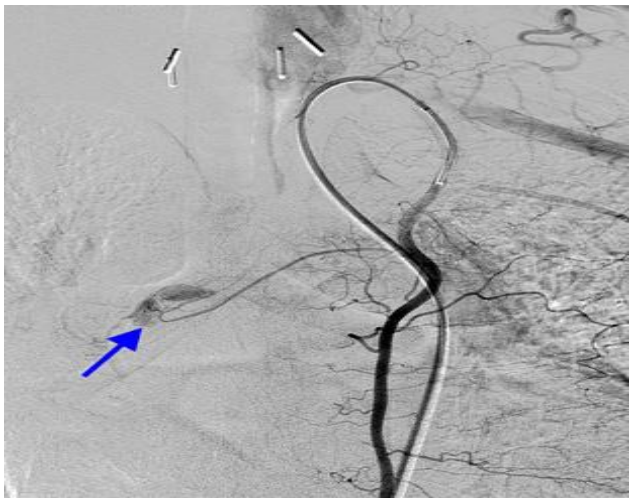


Figure 16: Selective parathyroid angiography with ectopic parathyroid tumour (arrow)
(Source: http://www.endocrinesurgery.net.au)

Despite their significant contribution to pre-operative planning, such techniques are linked with a number of risks, such as groin haematoma, contrast-induced anaphylaxis, contrast-induced acute renal failure and stroke, and should therefore be employed cautiously and only for the aforementioned indications.

10. INTRA-OPERATIVE PARATHYROID HORMONE (PTH) MEASUREMENT

With modern MIP techniques, not all parathyroid glands are visualised, as was the case with BNE. Therefore, with such focused approaches, an adjunct has to be used that enables the surgeon to be confident regarding the successful outcome of the operation prior to its termination. In other words, this means confirmation that the gland excised is indeed pathological, and that no remnant hyperfunctioning parathyroid tissue is left behind. This was achieved with the introduction of intra-operative measurement of PTH levels shortly after excision and removal of the diseased gland.

This is possible, since the half-life of PTH is very short, 2-4 minutes on average (3). According to Miami criteria, which are the most widely accepted, more than 50% drop from the highest pre-incision or pre-excision PTH level intra-operatively, ten minutes after removal of the parathyroid gland(s) confirms successful excision of all pathological tissue (32) (Fig.17). More specifically, in the case of a solitary parathyroid adenoma, there is a steep curve in PTH level reduction, with a plateau near the lower end of the normal range. Conversely, in multiglandular disease, PTH curve will be less steep, with a plateau at elevated levels, or at the upper limit of normal levels, thus warranting further exploration (4). Intra-operative PTH levels (IOPTH) may guarantee successful parathyroidectomy in up to 97%-99% of cases (2).

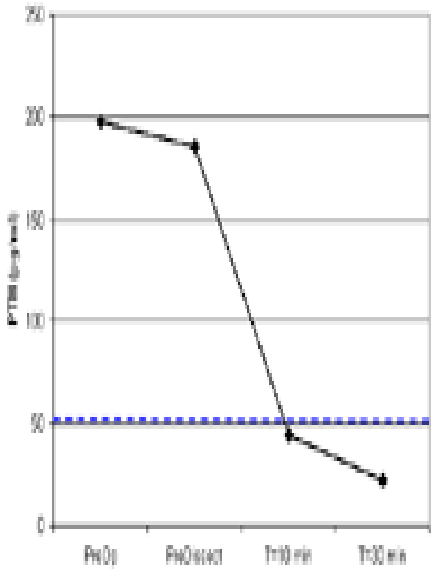


Figure 17: Miami criteria for IOPTH (Source: https://www.uclahealth.org)

A series of studies confirm the significance of intra-operative PTH (IOPTH) measurement for the successful outcome of MIP. Despite several debates regarding the cost-effectiveness of the method, it has been shown that IOPTH improves cure rates in such patients. In a study by Chen et al (33), all patients who had IOPTH measurement were cured, in contrast to those who were operated without subsequent IOPTH testing, among whom 10% had persistent hyperparathyroidism post-operatively. What is more, IOPTH changed the surgical planning from MIP to BNE in 10% of the patients who failed to show a satisfactory drop in IOPTH levels as defined by the Miami criteria.

Another study aimed to determine whether IOPTH testing is necessary in patients with concordant ultrasound and sestamibi scans (34). The researchers concluded that 6% of patients with concordant results had intra-operative findings which were inconsistent with pre-operative imaging. In that sense, IOPTH levels provide

indispensable information and should be used even in cases of concordant pre-operative imaging results.

This significance is even more highlighted in cases of discordant localisation studies, where IOPTH may alter operative management in up to 74% of patients (35). In the same study by Lew et al, the benefit of IOPTH in patients with concordant localisation was deemed marginal, with only 2% of patients undergoing a different surgical approach due to IOPTH findings.

Nevertheless, a recent retrospective review by Najafian et al aimed to prove that IOPTH testing may not be necessary for patients with only one positive, or else only indeterminate pre-operative localisation modalities (36). According to their findings, the operative management was modified in only 3% of these patients, while the cure rate is the same for patients with only one positive pre-operative localisation modality (96%), as well as those with two or more indeterminate modalities (100%).

Despite such findings, which of course require further confirmatory studies to take place, the role of IOPTH is vital in MIP. In terms of surgical approach determination, focused versus BNE, IOPTH is perhaps much more valuable in cases of equivocal pre-operative localisation findings, as opposed to those with strongly positive or negative findings (37). However, according to current guidelines, IOPTH is strongly indicated for all patients who undergo MIP for pHPT, regardless of pre-operative imaging concordance (2,33,34). If this practice is to change, for instance for cases gaining only marginal benefit from IOPTH, as described above, this will require extensive studies and adequate evidence. This is because the assurance provided by this method and its reliability are very hard to rival.

11. OTHER SURGICAL ADJUNCTS

Despite IOPTH being the most popular confirmatory test for resecting all hyperfunctioning parathyroid tissue, other adjuncts exist as well. For instance, frozen section analysis and ex vivo parathyroid aspiration may be employed (2). With frozen section assessment of the specimen, the pathologist aims to predominantly determine whether the tissue excised is actually parathyroid, and additionally attempts to differentiate hyperplasia from carcinoma, which is however more challenging. As far as ex vivo parathyroid aspiration and subsequent IOPTH assay is concerned, this is deemed to be an accurate way of distinguishing parathyroid from non-parathyroid tissue (38). Other adjuncts may be used, some that aid gland visualisation (methylene blue, near infrared fluorescence and infrared spectroscopy), and others that assist in gland localisation (intra-operative ultrasonography, gamma-probe guidance and bilateral jugular venous sampling).

PART II

TARGETS AND ASSUMPTIONS

This systematic review aims to demonstrate the establishment and increasing significance of minimally invasive surgery, and in particular MIVAP, for the treatment of pHPT. Indeed, as the surgical approach to this condition continuously evolves, it is of crucial importance to show whether modern operative techniques truly benefit patients, and therefore whether a shift from classical BNE to MIP is justified, based on solid bibliographical evidence. What is more, this review concentrates on the role of MIVAP and attempts to make an objective comparison of this technique with other minimally invasive methods, such as open, focused parathyroidectomy, totally endoscopic parathyroidectomy, and others that have previously been briefly mentioned. In other words, the principal target of this review is to clarify the potential advantages of MIVAP (and hence other MIP techniques) over BNE, and in addition, to demonstrate whether or not, and in what way MIVAP supersedes other minimally-invasive techniques for surgical management of pHPT.

A systematic analysis of current literature will be made, aiming to ground our findings on solid evidence-based knowledge, and so contribute to steering modern surgical practice in the treatment of this common endocrine disorder. Due to the relative novelty of these techniques, which have emerged over the last two decades, the number of studies attempting a thorough analysis and comparison of these is limited, while new studies are steadily being published. And while the superiority of minimally-invasive parathyroid surgery is undisputable for solitary parathyroid adenomas, clearly localised by one or more pre-operative imaging modalities, further research is needed in order to ascertain whether MIP could be indicated for other causes of pHPT as well. Therefore, it would be valuable to investigate existing literature for studies attempting to employ such techniques for cases of multiple adenomas, multiglandular disease, or familial pHPT, and so widen the horizons of future surgical practice.

Furthermore, minimally-invasive techniques for parathyroidectomy share many common features in terms of cosmetic outcome, patient satisfaction and rapid post-operative recovery, however each of them has special characteristics. Delineating such subtle differences may be important for deciding which modality could be more reliably used for certain cases. Nevertheless, very few existing studies provide an inclusive and thorough presentation and comparison of all these techniques in one study. Thus, it is evident that this systematic review will contribute significantly to forming an objective opinion about these techniques, stressing their comparative advantages and drawbacks, as well as ascertaining cases where one might supersede in certain aspects. Most importantly, motivation for future research will be generated, in order to achieve potential expansion of their therapeutic indications, and make clearer recommendations on which technique to use for specific pathologies and locations of pathological tissue.

This is particularly significant for MIVAP, one of the most popular minimally invasive modalities. MIVAP currently has a continually emerging place in parathyroidectomy for pHPT, possessing the predisposition to be employed in more complex cases, for instance familial or multiglandular disease, as it enables the surgeon to perform bilateral cervical exploration through a minimal midline incision. As it is easily understood, concentrating on the role of this technique as well as its future perspective is particularly interesting for the management of this common endocrine disorder. Evidence is required to assess not only whether it is superior to classical BNE, but more importantly, to determine whether it is more reliable than the remaining MIP techniques.

This comparison will be the central goal of this review. However, by carefully investigating existing literature, the aim is not only to compare MIVAP with the aforementioned techniques, traditional or minimally-invasive, but also to clarify the precise patient and disease characteristics where it may have some, if any, additional benefit. In this way, the current review aims to confirm current indications for MIVAP, but also to search for others, empowering the surgeon to assess whether this promising video-assisted method can be used for a wider spectrum of patients and disease features, and various locations and extent of hyperfunctioning parathyroid tissue.

Bearing all the above in mind, the main hypothesis on which this systematic review was based is that MIVAP is actually superior to BNE for the surgical treatment of pHPT, having at least equal cure rates and morbidity, as well as additional advantages in terms of cosmetic outcome, pain, post-operative recovery, length of hospital stay, and patient satisfaction. This has been well-established already for cases of solitary parathyroid adenomas, but the present review seeks to prove the technique's benefits for additional causes of pHPT. What is more, this study aims to prove through thorough literature research that MIVAP should be preferred over the other MIP techniques, for instance OMIP, especially for specific disease characteristics, such as multiglandular disease or cases with concurrent thyroid pathology.

These two basic hypotheses will be the foundation of this research, and given its novelty in that it includes a comparison of all modern surgical techniques in parathyroidectomy in one study, it will contribute to shaping an objective view on the management of pHPT and motivate future researchers to further investigate this interesting subject, in order to confirm or contradict the current findings.

MATERIAL AND METHODS

This study is a systematic review of medical literature on the role of MIVAP in the surgical management of pHPT. It seeks to analyse existing studies on this field, explain their findings and then proceed to an objective comparison among them. For this purpose, an extensive search was performed on Pubmed, the on-line database for

biomedical literature (www.ncbi.nlm.nih.gov). All articles, reviews and studies which were employed for the accomplishment of this research were included in the aforementioned database, hence proving their credibility and recognition. All of these were written in the english language.

A detailed investigation took place, involving articles containing the words "MIVAP" and "primary hyperparathyroidism", aiming to seek for publications in globally recognised medical journals. Fourteen studies performed a direct comparison between MIVAP and open BNE, while eight additional studies compared the former with the remaining minimally invasive techniques for parathyroidectomy, and especially OMIP. Moreover, fourteen other studies contemplated an analysis of other minimally invasive modalities, including a comparison with traditional parathyroidectomy or MIVAP (but none of them performed a comparison among all the techniques). A careful analysis of these ensued, recognising their limitations and potential bias. The target was to include articles covering various aspects, not only other minimally-invasive techniques, apart from MIVAP, but also a wide spectrum of issues, for instance complications, effectiveness, anaesthetic implications, cost, operative time and length of hospital stay. This resulted in a systematic review which addresses the subject in question from a multi-dimensional perspective, aiming to reach valuable conclusions for current and most importantly future surgical practice on the treatment of pHPT.

RESULTS

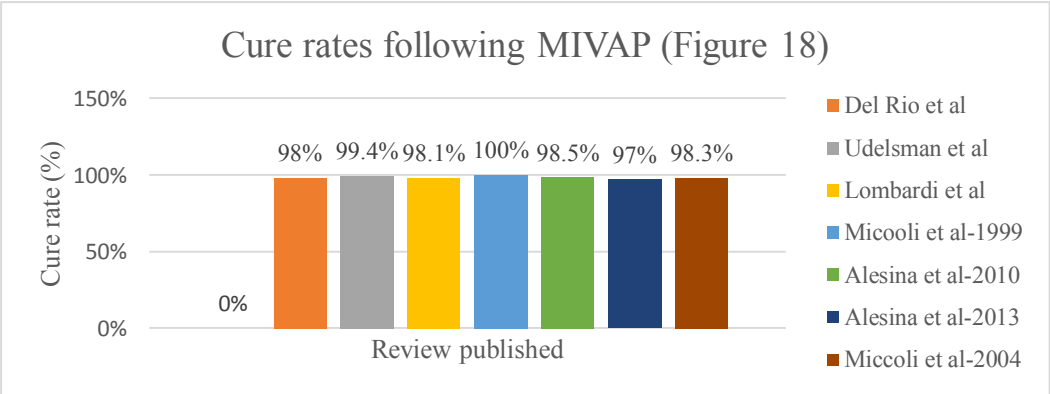
To start with, Del Rio et al published their findings from a retrospective review of a prospectively collected database of 157 patients undergoing either MIVAP with IOPTH measurement or traditional BNE with cervicotomy and intra-operative frozen section for pHPT (39). They demonstrated that MIVAP with IOPTH was associated with a statistically significant shorter operative time versus BNE (29 vs 62 min). In addition, patients in the MIVAP group reported reduced post-operative pain, and this was assessed both one and twenty-four hours after the operation. Likewise, this proved to be statistically significant. On the other hand, post-operative calcium levels, and rates of relapse or post-operative dysphonia were similar between both groups. In three patients of the MIVAP group the pathological gland localised on pre-operative imaging was not recognised intra-operatively, and thus video-assisted BNE ensued, while conversion to open BNE was required for only four patients (5%). Reduced post-operative pain reported with MIVAP was attributed by the authors to minimal tissue dissection and avoidance of neck hyperextension. For the MIVAP group, the exclusion criteria were set as: those with pathological gland >3cm in diameter on pre-operative imaging, family history of parathyroid disease, previous cervical operations, and suspicion of parathyroid carcinoma or concurrent inflammatory thyroid condition. The authors also stress the significance of the fact that MIVAP allows for video-assisted BNE, thus reducing conversion rates to open BNE and achieving exceptional

cure rates even with equivocal or absent IOPTH results. This along with the ability of MIVAP to allow for treatment of concurrent thyroid goitre differentiate this method from the remaining MIP techniques.

Another retrospective review by Udelsman et al attempted to compare minimally-invasive parathyroidectomy with traditional BNE in a large group of patients (40). The researchers used a pool of 1650 patients, divided between the two different approaches, to examine whether there was any noticeable difference in terms of cure rates, complications, length of stay in the hospital and total costs. According to the findings, MIP improves cure rates compared to classical BNE (99.4% versus 97.1%), and causes fewer complications (1.45% versus 3.10% respectively). The advantage of MIP over BNE was maintained even when the comparison involved length of hospital stay and total costs. All in all, the researchers concluded than MIP supersedes open traditional BNE in the management of pHPT, when employed for particular indications.

Such results have been confirmed by another study (41), which again compares MIP with BNE. MIP was found to be correlated with shorter operative time and length of stay in hospital, together with a smaller incision, thus guaranteeing better cosmetic outcome. In addition, MIP may be performed with ease under local anaesthetic and is not linked with as many complications as traditional BNE. The authors, however, stress the fact that MIP is dependent on reliable pre-operative localisation imaging, in their case sestamibi scan.

The superiority of video-assisted parathyroidectomy over traditional cervicotomy has also been demonstrated by Lombardi et al (41), with regards to patient satisfaction, cosmesis and post-operative pain. MIVAP achieved a cure rate as high as 98.1% (Fig. 18). Moreover, the authors stress the importance of the technique's ability to perform bilateral neck exploration endoscopically. In addition, its greater resemblance to traditional open BNE compared to other MIP techniques, the feasibility of treating concurrent thyroid pathology as well as the opportunity it provides for loco-regional anaesthesia have rendered this approach advantageous for management of pHPT, and in particular for treatment of well-localised parathyroid adenomas.

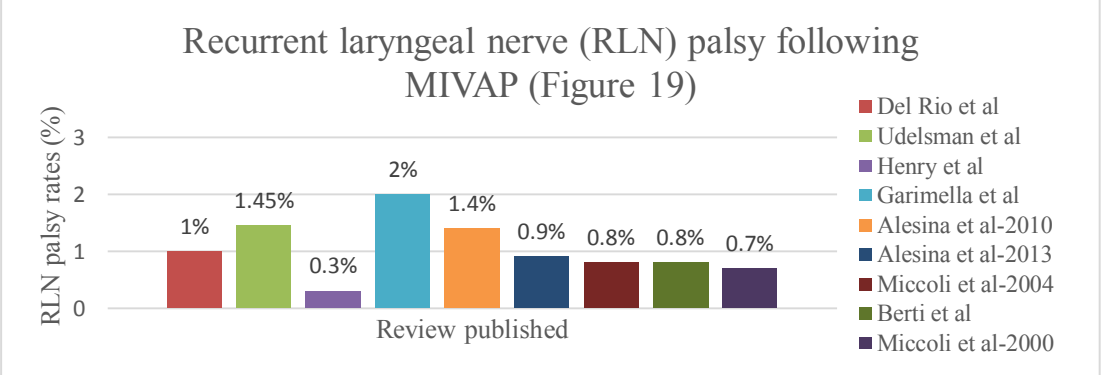


Another retrospective review of 528 patients aimed to compare video-assisted parathyroidectomy (either as MIVAP for anteriorly located adenomas or as VAPLA

for adenomas sited deeply in the cervix) with BNE (42). Patients who were deemed unsuitable for video-assisted parathyroidectomy (43% of the participants) were those with simultaneous presence of a nodular goitre, preceding cervical operation, suspected multiglandular disease and discordant or absent pre-operative localisation studies. For the remaining cases, who were submitted to MIVAP or VAPLA, mean operative time was 50 minutes, ranging from 20 to 130 minutes, and conversion to traditional BNE was needed in 14% of cases. The main reasons necessitating conversion to an open procedure were missed adenomas, laborious dissection, presence of multiglandular disease implied by inadequate drop of IOPTH levels, false negative IOPTH levels, and misleading pre-operative localisation by sestamibi or ultrasonography. In terms of complications, only one patient sustained RLN damage, while two more patients developed persistence or recurrence of their disease. Overall, this study showed that video-assisted parathyroidectomy may be regarded as being at least equal to its traditional rival.

Lombardi et al performed a search in Pubmed in 2009 (43), in order to trace existing studies on the emerging role of MIVAP in the management of pHPT. Their findings confirmed that MIVAP is associated with better cosmetic outcome, reduced post-operative pain, a more rapid recovery and increased patient satisfaction, while sharing similar complication rates as traditional parathyroidectomy. The authors also stated that the contribution of MIVAP to multiglandular disease, for instance in cases of familial or secondary hyperparathyroidism, needs further research for safe recommendations to be made.

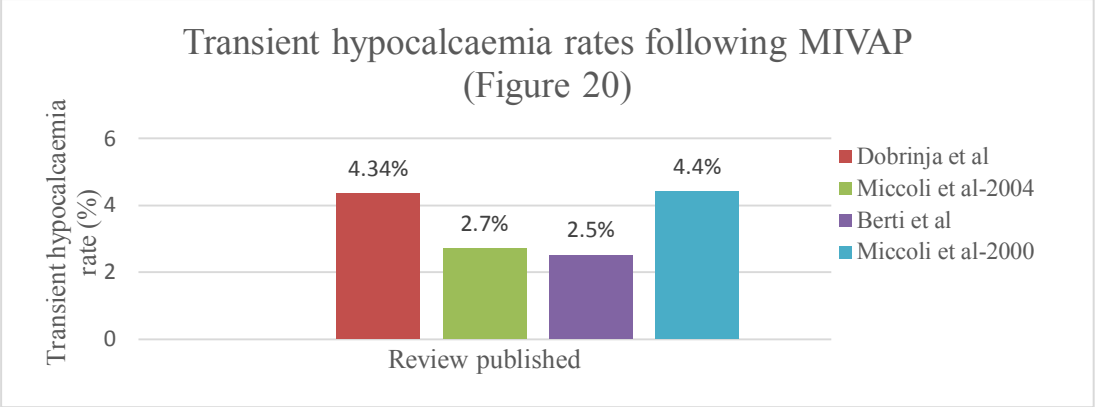
The safety and efficacy of MIVAP, together with the opportunity it provides for video-assisted bilateral cervical exploration have been shown in a multitude of studies, like the own published by Garimella et al (44). This study included a series of 56 patients who underwent MIVAP for pHPT over an 8-year period, after localisation of the hyperfunctioning gland by ultrasound and sestamibi. The mean operating time was 78 minutes, and like in other similar studies, conversion rate to open BNE was 14%. The basic reasons for conversion were unsuccessful exploration, difficulty to retrieve a spacious, friable adenoma, as well as the presence of a very small adenoma. Only one patient suffered from complications, in the form of temporary RLN palsy, while all patients had post-operative calcium levels within normal range, apart from 5 individuals (Fig. 19).



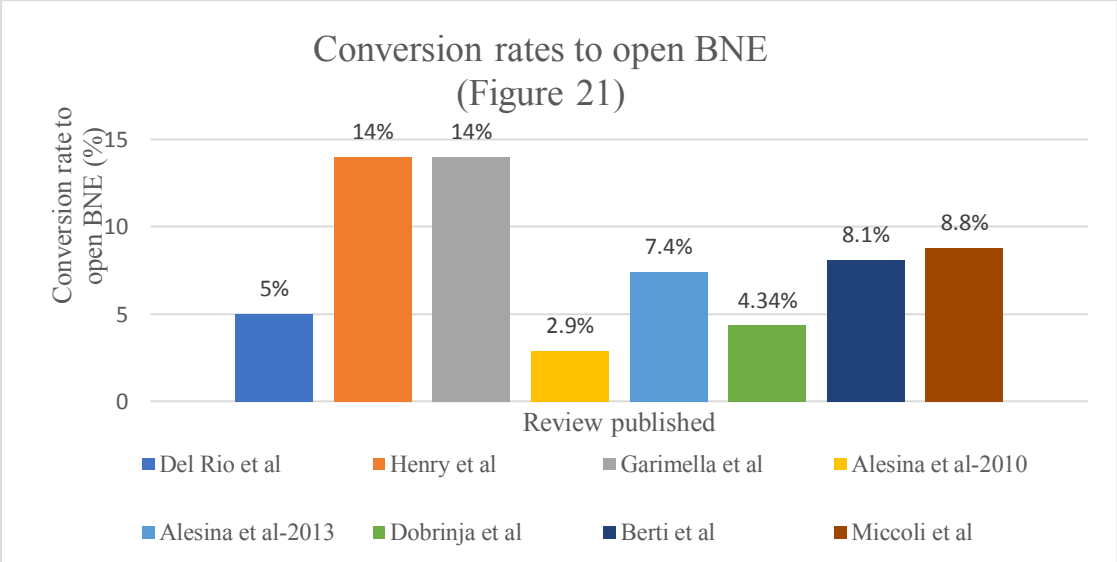
In a prospective randomised study, Micolli, the father of MIVAP, attempted to compare his technique to traditional BNE, by allocating 38 patients to either of these techniques (45). In the group of patients who underwent MIVAP, IOPTH levels were also measured in order to confirm the successful outcome of the operation. The authors wished to demonstrate whether MIVAP actually supersedes BNE in terms of cosmesis, operative time, post-operative pain and calcium levels. It was shown that the operative time was significantly reduced with MIVAP, which lasted for 57 minutes on average, as opposed to traditional cervicotomy and bilateral exploration, which had a mean operative time of 70 minutes. The cosmetic outcome with MIVAP was superior, and what is more, these patients suffered from less post-operative pain, and that proved to be statistically significant. All patients in both groups became eucalcaemic after the operation, with no persistent primary hyperparathyroidism reported. However, RLN palsy was reported in one case from the MIVAP group. Overall, these findings are consistent with those from other studies, which agree that MIVAP provides better cosmetic results, with improved patient satisfaction and reduced post-operative pain.

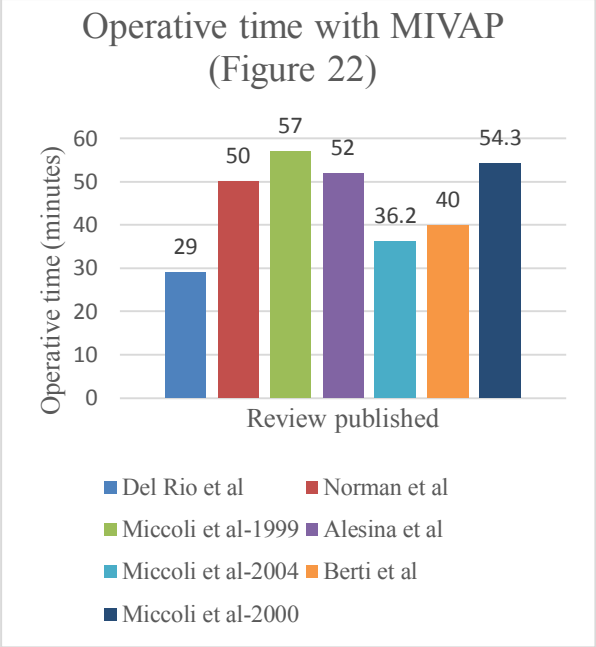
A very interesting study regarding the opportunity given by MIVAP for endoscopic bilateral exploration of the neck was published by Alesina et al (46). The authors begin their rationale for the study by stating that pre-operative accurate localisation of the hyperfunctioning parathyroid gland has thus far been considered an indispensable condition for MIP. Indeed, in cases of failed localisation of pathological tissue pre-operatively, open BNE is regarded as the most widely accepted technique. Nevertheless, this study attempted to examine the reliability of video-assisted BNE performed by MIVAP, for cases of discordant or negative pre-operative imaging. This was studied in a pool of 68 patients, and the outcomes concerned operative time, conversion to open BNE, complications and cure rate. The operative time ranged from 20 to 180 minutes, with a mean time of 52 +/- 26 minutes, and MIVAP with video-assisted BNE was successful in 97% of cases. Only two patients required conversion to an open procedure. Up to 98.5% of patients were cured biochemically, while only one of them had persistent hyperparathyroidism even after re-exploration done by MIVAP. Moreover, only one patient was reported to have RLN palsy. As a result of these findings, the authors concluded that MIVAP with video-assisted BNE was equally safe and effective as traditional, open BNE for patients with pHPT and discordant pre-operative localisation findings.

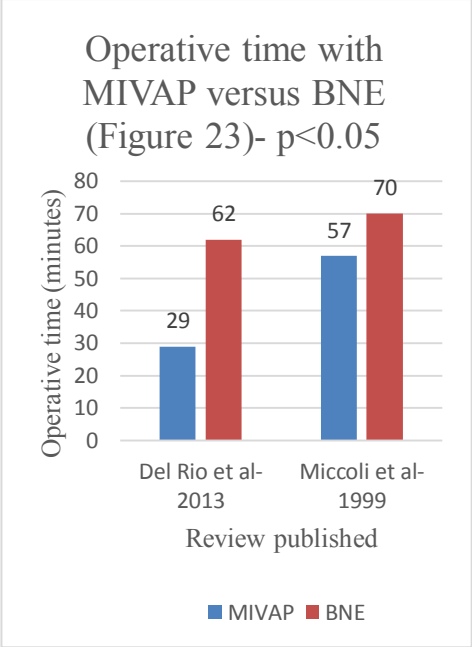
Three years later, Alesina published a new study in order to confirm his findings, and indeed, he reached the same conclusion (47). This was based on a sample of 107 patients, and the authors found that biochemical cure was achieved in 97% of these patients. Only 8 conversions were required to traditional cervicotomy, while there was only one case of permanent RLN damage and three cases of persistent or recurrent hyperparathyroidism (Fig. 20).



Such results are reinforced by findings from other studies, which all lead to the same conclusion: that MIVAP is equally safe and curative as traditional BNE, with significantly superior cosmetic outcome and post-operative parameters. Cure rates are consistently being reported as high as 98% (Fig. 18), while complication rates are kept to a minimum, ranging from 2.7-4.4% for post-operative transient hypocalcaemia (Fig. 20), and less than 1% for RLN palsy (48-51)(Fig. 19). Persistent hyperparathyroidism is rarely (2.1%) encountered after MIVAP (50). More than 90% of patients undergoing MIVAP were satisfied with the cosmetic result in a series of reviews by Miccoli et al, following two and six years of MIVAP experience (49, 51), while conversion rates were roughly around 4%, as reported by Dobrinja et al (48). Nevertheless, some authors report conversion rates of 8-8.8% (50, 51) while in some cases it may reach up to 14% (44) (Fig. 21). Mean operative time may be as short as 36 minutes with MIVAP (Fig. 22,23), while simultaneous thyroid lobectomy or total thyroidectomy may be concurrently performed (49). This has been particularly hailed by Miccoli and his colleagues, as well as the fact that MIVAP provides the opportunity for performance under loco-regional anaesthesia, with profound positive outcome for the patient.







What is more, Miccoli has also attempted to use MIVAP for a case of familial hyperparathyroidism, being able to perform subtotal parathyroidectomy and cervical thymectomy (20). This was again due to MIVAP's ability for bilateral exploration of the neck. Furthermore, MIVAP has also been described to achieve subtotal parathyroidectomy even for cases of secondary hyperparathyroidism, as shown in a review by Barbaros et al (52). It is also known that one of the most common exclusion criteria for MIVAP in virtually all studies is the suspicion of parathyroid carcinoma. However, in a study by Bakkar et al (53), MIVAP involving a simultaneous en block thyroid lobectomy was successfully performed for a patient for whom a suspicion of parathyroid carcinoma had been raised. This has prompted the authors to think whether this technique should be used in a broader variety of cases, expanding its indications. Nevertheless, according to current guidelines, MIVAP is indicated only for cases of pHPT caused by a solitary well-localised parathyroid adenoma, and so these findings constitute a solid foundation for future research on this aspect.

In addition to all these findings concerning MIVAP and its predominant role in treating primary hyperparathyroidism, a variety of other studies aim to demonstrate the importance of other minimally invasive procedures for the management of this common endocrine condition. To start with, in a review by Henry et al (18), video-assisted parathyroidectomy by lateral approach (VAPLA) was used in 166 patients, excluding among others those with concomitant thyroid disease and suspected multiglandular involvement. Conversion to BNE was performed in 15.6% of patients and morbidity rate was kept to a minimum, with only one permanent RLN palsy. Thus, it was assumed that VAPLA is safe, effective and ideal for solitary adenomas that are small and adequately localised pre-operatively. In another retrospective review by Henry et al (54), VAPLA again showed similar results to traditional BNE, with satisfactory visualisation of neck structures, being suitable for adenomas located deeply in the cervix, or situated in the upper and posterior mediastinum, usually

concerning the superior parathyroid glands. However, the level of contraindications for VAPLA was higher to that of MIVAP (43% vs 29%), since the latter was additionally used for cases of simultaneous thyroid disease or discordant findings on pre-operative imaging, as VAPLA cannot accomplish bilateral exploration of the neck (16, 54).

Moving on to minimally invasive radio-guided parathyroidectomy (MIRP), in a review by Goldstein et al (13), twenty patients who underwent this method were compared to twenty patients who had conventional parathyroidectomy. It was shown that operative time, operative charges and total hospital costs were decreased at a significant extent in patients submitted to MIRP. No failures in the biochemical treatment of pHPT were noted, and no complications were seen. As many as 65% of these patients were able to leave the hospital five hours after the procedure. What is more, MIRP was performed in a multitude of cases under loco-regional anaesthesia, while also avoiding the need for IOPTH level measurement, since the hand-held probe allows for satisfactory confirmation of the hyperfunctioning parathyroid gland. Thus, the reduction in operative time and costs is easily explained. Indeed, the fact that IOPTH measurement or frozen sections are not required during MIRP is particularly stressed in a review by Murphy et al (55). Furthermore, MIRP has been shown to be very effective for patients with previous thyroid or parathyroid surgery. The technique is associated with a directed dissection, which minimises the length of the scar, and allows for use of local anaesthesia, while providing excellent results for re-operative neck in a review by Norman et al (41). Nevertheless, in a study by Burkey et al (56), comparing the gamma probe and IOPTH, it was shown that identification of parathyroid adenomas by the former occurred in 66% of patients, and intra-operative confirmation of cure reached 84%, whereas IOPTH measurement showed adequate (ie more than 50%) decrease in 98% of cases. Thus, the use of a gamma probe was demonstrated to be an inconsistently reliable tool for localisation of primary parathyroid pathology, while IOPTH was shown to reliably predict successful operative outcome.

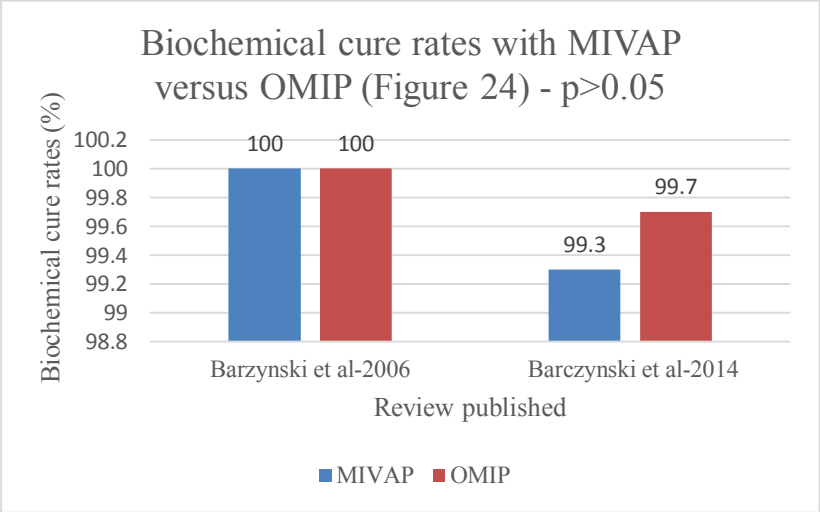
When it comes to total endoscopic parathyroidectomy (EP), first described by Gagner, a number of studies confirm its excellent cosmetic results and establish its position as an alternative to traditional parathyroidectomy. In 1998, Yeung et al showed that EP increases patients' satisfaction as a result of the shorter scar length, while causing little post-operative pain (57). Three years later, Cougard et al published their prospective review of 100 endoscopic parathyroidectomies. To perform these, a central trocar was placed in the midline of the neck, where the endoscope was inserted, followed by insertion of two more, laterally-sited trocars. Subsequently, the neck was inflated with gas to provide an operative field. Eucalcaemia was achieved in 96% of patients post-operatively, while the cosmetic outcome was exceptional. Furthermore, no complications were noted, and mean length of hospital stay was 24 hours. Conversion to open cervicotomy was required in 15% of the patients, due to either negative exploration or multiglandular hyperplasia. As a result, the authors

conclude that EP is a safe method, which additionally provides the opportunity for bilateral exploration of the neck in experienced hands (58). Moreover, EP has been performed by gas insufflation of the cervix or by a gasless technique, with equally satisfying results (59, 60). Indeed, the substitution of carbon dioxide insufflation by a gasless, skin-lifting approach eliminates probable complications associated with gas, while ensuring direct manipulation of tissues and a high cosmetic result (60). This was achieved by making an incision below the clavicle and another one on the lateral side of the neck, in order to lift the skin.

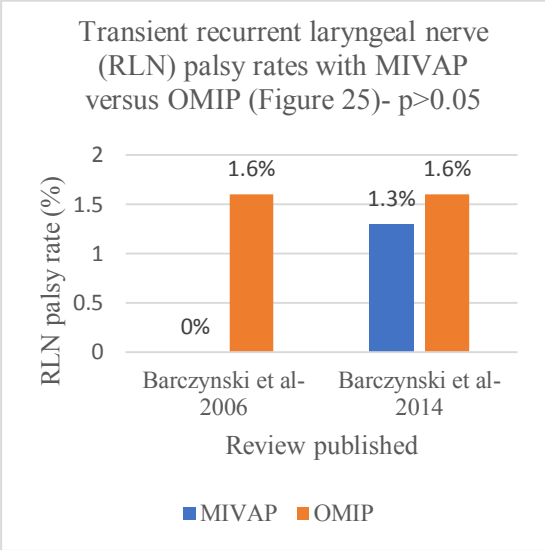
In addition, a number of extra-cervical approaches have been described, from either the chest wall, the axilla or the breast (16). Although such approaches provide perfect cosmetic outcome, with almost invisible scars, they are associated with a greater degree of invasiveness and deeper dissection of tissues, and so more complications. What is more, they tend to lengthen the duration of the procedure, and in addition, they are correlated with a number of complications due to carbon dioxide absorption.

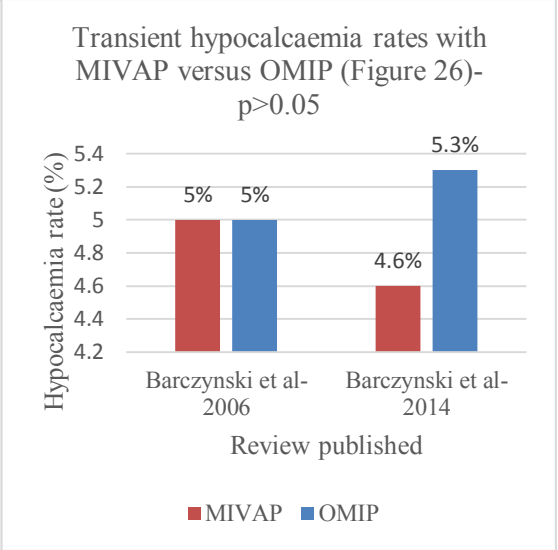
The next minimally invasive approach for parathyroidectomy, which along with MIVAP is the most popular, is open minimally invasive parathyroidectomy (OMIP), using a small incision over the hyperfunctioning gland. In a review by Pitale et al (61), OMIP was proven to be equally effective as traditional BNE in the treatment of pHPT. The authors included patients whose adenoma had been adequately localised pre-operatively. Conversion to BNE was required in only two out of 24 patients, due to failed identification of the adenoma through the small incision. The mean operative time was 49 minutes, and all patients achieved biochemical cure of their hyperparathyroidism. No post-operative hypocalcaemia was noted, and one patient had temporary RLN palsy. In another randomised clinical trial by Russell et al (62), one hundred patients with a localised parathyroid adenoma were randomised to either BNE or OMIP. All patients were eventually cured, while only two patients who underwent BNE were found to have an additional unsuspected pathological gland on the other side. Thus, it was concluded that the rate of persistent hyperparathyroidism did not differ significantly between the two groups. Furthermore, Udelsman et al described the results of 255 patients who were treated by OMIP, compared to 401 others who underwent traditional BNE (15). For the first group, cervical block anaesthesia was employed, whereas the latter group was operated under general anaesthesia. Both methods had no statistically significant differences with regards to cure rates and complications. Nevertheless, OMIP was superior to BNE in that it was associated with a shorter operative time and length of hospital stay, greater patient comfort and reduced costs. Such findings are reinforced by other studies (63, 64) which state that selected patients with sporadic pHPT are suitable for OMIP, which constitutes a cost-effective alternative to traditional BNE, with the exception of those with multiglandular disease or MEN syndrome.

After establishing the clear benefit of minimally-invasive techniques, and especially MIVAP for the treatment of pHPT, it is of particular interest to search current literature for a comparison among them, looking for any potential advantages of MIVAP over the others. It is true that the majority of such reviews attempt a comparison between MIVAP and OMIP, however in some of the aforementioned studies, it is easy to trace certain advantages of MIVAP over the others, particularly in terms of bilateral exploration of the neck and treatment of concomitant thyroid pathology. Undoubtedly, one of the studies that constitutes a landmark for this research is the one published by Barczynski et al in 2006 (65), comparing MIVAP with OMIP for cases of solirary parathyroid adenomas. This was a prospective, randomized, blinded clinical trial, involving 60 patients, equally distributed in the two groups. IOPTH level measurement was used to confirm successful operative outcome. Interestingly, all patients in both groups were cured of their hyperparathyroidism (Fig.24). Of note is the fact that in two cases where an inadequate drop of IOPTH necessitated further exploration, this was performed without conversion to an open classical BNE, either by video-assistance (one case in the MIVAP group), or unilateral neck exploration (one case in the OMIP group). What is more, no statistically significant difference was traced in terms of operative time (median time 44.2 minutes versus 49.7 minutes for OMIP), and the same applies for rates of transient hypocalcaemia or RLN palsy (Fig. 25,26).



On the other hand, it was found that patients who underwent MIVAP suffered from less severe post-operative pain, as assessed by the visual analogue scale (VAS), at 4,8,12 and 24 hours after the operation, and that proved to be statistically significant. As a natural consequence of this, these patients requested analgesia at a lesser extent, and consumed smaller quantities of analgesics (in this study ketoprofen), than those who underwent OMIP (Fig. 27). Furthermore, patients in the MIVAP group reported superior quality of their life during the early recovery period after their operation, as evaluated by the SF-36 questionnaire, in terms of physical functioning and bodily pain. In addition to these findings, patients having MIVAP had smaller scars (17.2mm versus 30.8mm on average), as well as superior rates of cosmetic satisfaction one month after the operation.

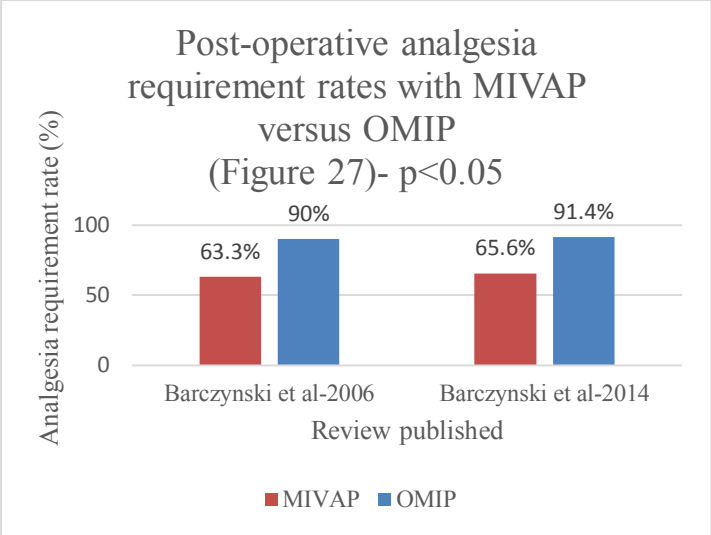


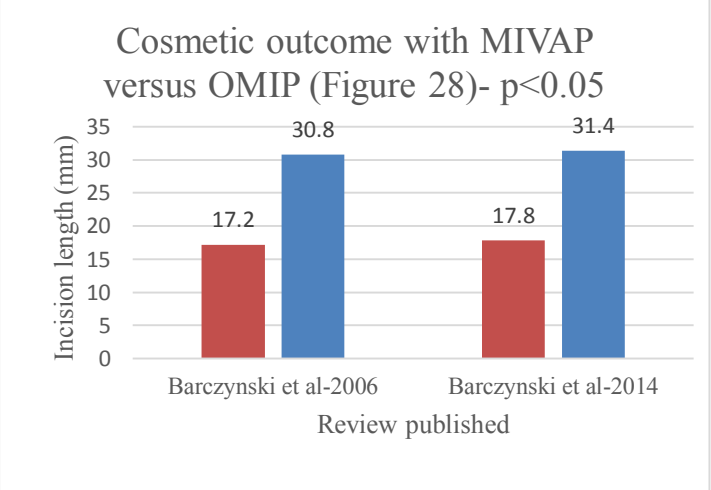


However, MIVAP was more expensive than OMIP, and this proved to be because of additional costs associated with endoscopic equipment. Patients from both groups did not differ significantly in terms of length of hospital stay, and had similar serum calcium and PTH levels during a follow-up period of six months. Thus, the authors found that both these methods provide a reliable therapeutic option for pHPT caused by a single parathyroid adenoma, and are associated with very low rates of morbidity. At the same time, MIVAP offered a wide range of advantages, in terms of cosmetic outcome, post-operative pain and physical function, as outlined earlier, while facilitating recognition of the RLN.

In order to further investigate this issue and perform a more objective comparison of these two techniques in a larger pool of patients, Barczynski et al published a retrospective, case-control analysis on this issue (66) in 2014. In total, 455 patients were submitted to either of these techniques in this study. Patients with previous cervical surgery, neck irradiation or radioiodine treatment in the past, multinodular goitre, suspected multiglandular parathyroid disease or parathyroid carcinoma, as well as those with familial hyperparathyroidism and suspected MEN syndrome were excluded from the study.

In absolute accordance with the previous study, it was again demonstrated that MIVAP was associated with significantly reduced levels of post-operative pain at 4, 8, 12 and 24 hours after the operation, as assessed by VAS. The difference in pain intensity reached even 32.7% twenty-four hours after surgery. As stated by the authors, this was not only explained by the shorter incision length and smaller extent of tissue damage accompanying MIVAP, but also due to avoidance of intra-operative neck hyperextension with this method. There was also a statistically significant drop in request rates for analgesia in patients undergoing MIVAP (65.6% versus 91.4%), as well as a reduction in mean consumption of analgesics (Fig. 27). In addition to these findings, MIVAP was more reliable for identification of the RLN (92.7% versus 72.7%), as it allows for magnification of the nerve up to ten times, although the prevalence of RLN damage did not differ significantly between these methods.





Moreover, patients were much more satisfied with their cosmetic result after MIVAP, both one and six months after the operation, as indeed, the scar was much smaller in this group (17.8mm on average versus 31.4 mm) (Fig. 28).

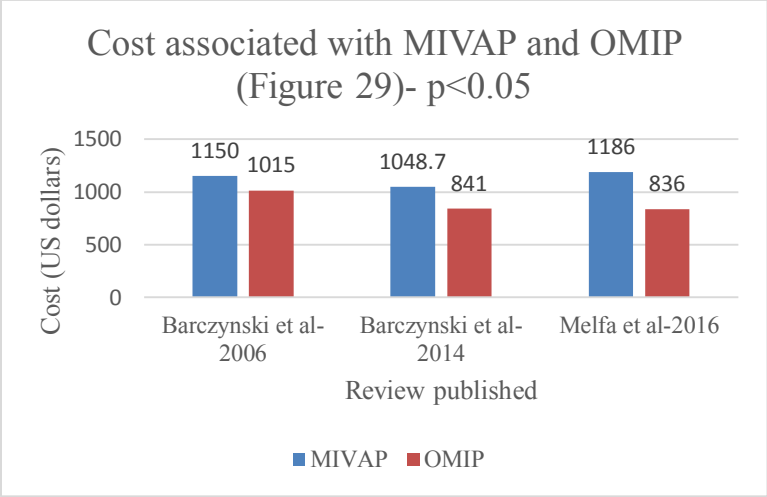
On the contrary, OMIP was associated with a significantly reduced operative time (on average 37.4 minutes versus 42.5 minutes). In addition, MIVAP was 25% more expensive than OMIP, and this was primarily attributed to longer operative time and costs associated with the endoscopic equipment. Cure rates, morbidity and length of hospitalization were similar between the two groups (Fig. 24,25,26).

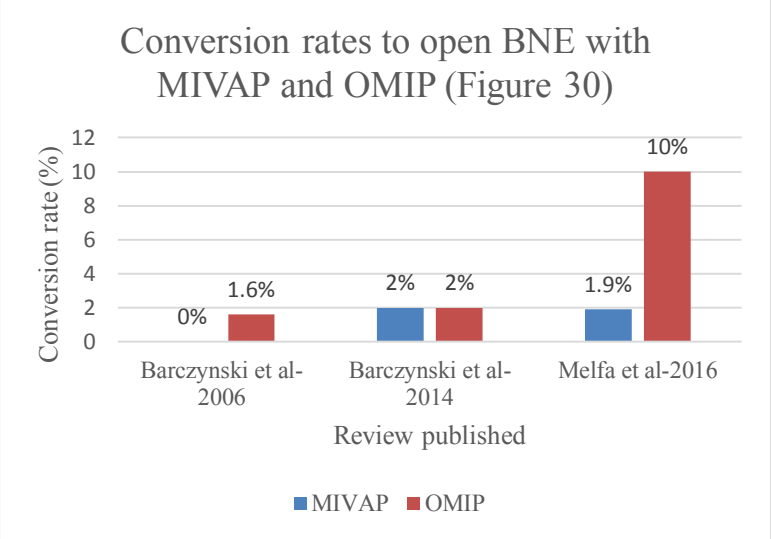
It is also pointed that both these techniques could be performed as day-case procedures under local anaesthesia, although this was not done in this study due to reimbursement-associated insurer's regulations. The authors also admit that their study is biased in that the selection of either MIVAP or OMIP was based on patients' preference, and so discrepancies in patient characteristics do exist between the two groups. Nevertheless, they assume that this fact has not influenced the credibility of their outcomes. In addition, they emphasise that the most important factor for the success of MIP is the surgeon's experience in it, and that adequate surgical experience in open BNE should be a prerequisite. They conclude by stating that MIVAP has significant advantages over OMIP in terms of post-operative pain, and cosmesis, but is more expensive than OMIP, and requires additional experience in endoscopic surgery.

Another study by Melfa et al (5) aims to compare patients undergoing OMIP under local anaesthesia with patients having MIVAP under general anaesthesia for pHPT, concentrating mainly on each technique's cost. In this study, OMIP was used for cases where pre-operative imaging suggested a single, orthotopic parathyroid adenoma, with concordant pre-operative US and sestamibi. On the other hand,

MIVAP was reserved for cases of discordant or non-diagnostic imaging prior to the operation, or for deep and posteriorly located adenomas, due to its ability to perform bilateral neck exploration at the same time.

In accordance with the aforementioned study by Barczynski et al, MIVAP performed under general anaesthesia was shown to be more expensive than OMIP performed under local anaesthesia, and that was found to be due to expenses associated with anaesthesia (general versus local) and equipment (need for endoscopic equipment in the case of MIVAP). However, the authors stress that due to MIVAP's ability to carry out bilateral neck exploration, a single pre-operative localisation method with a positive result could suffice, thus reducing cost (Fig. 29).





In another part of their study, the authors mention that OMIP, although it is indicated for excision of any parathyroid adenoma, was employed by them for treatment of inferior parathyroid adenomas rather than superior, due to their more superficial position with regards to the RLN. In this way, excessive traction with OMIP in order to reach deeper planes was avoided, even though there is no evidence so far that this technique has significant difference from MIVAP in terms of complications. On the contrary, MIVAP was reserved for treatment of superior parathyroid adenomas, as the researchers believed it to be safer for dissection into deeper planes. Moreover, conversion rate to conventional BNE for OMIP reached 10% of patients, whereas for MIVAP, it approached only 1.9% (Fig. 30).

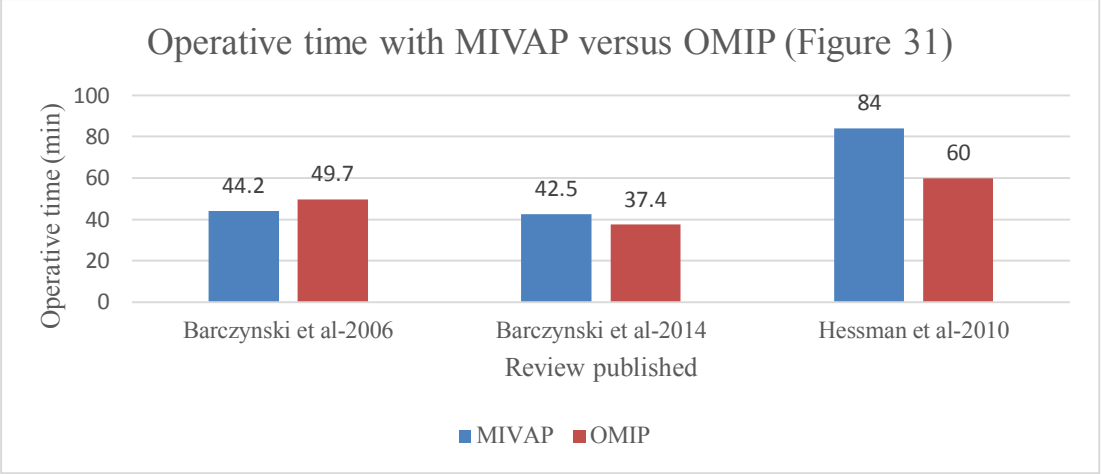
This study overall admits that both these methods are safe and effective for treatment of pHPT. Furthermore, while concluding that OMIP was shown to be cheaper than MIVAP in general, it points out that three important features need to be taken into

consideration. Indeed, although not performed for these patients, MIVAP may be done under local anaesthesia, thus eliminating anaesthesia-related costs. In addition, MIVAP offers bilateral cervical exploration, rendering the use of two concordant pre-operative imaging modalities potentially unnecessary and so further reducing cost. What is more, OMIP cannot be used in cases of concomitant thyroid disease and was associated in this study with higher conversion rates, thus justifying the use of MIVAP by the authors despite its superior cost.

Indeed, as it was demonstrated by Miccoli et al (21), MIVAP may not only be performed under regional anaesthesia, but it is also associated with shorter operative time (from induction of anaesthesia to return to the ward) and decreased post-operative analgesia requirement. In this study, patients who received regional anaesthesia (RA) for MIVAP had a bilateral deep cervical block, with local infiltration of the incision with a mixture of local anaesthetics, showing that MIVAP under RA is not only feasible, but is also correlated with significant advantages.

In 2012, Melck et al attempted a comparison of video-assisted and conventional minimally invasive parathyroidectomy for treatment of sporadic pHPT (67). This was a case-control study and compared 125 cases where the video-assisted technique was employed, with 95 cases treated by the conventional, open minimally invasive technique. The authors found that there was no significant difference between the groups in terms of mean operative time, analgesia requirement after the operation and complication rates. 14% of patients who underwent video-assisted parathyroidectomy (VAP) required conversion to open MIP. Overall, the authors state that VAP is safe and advantageous as far as cosmesis is concerned, and allows for shorter length of hospital stay, while maintaining low conversion rates.

A study that fails to demonstrate MIVAP's aforementioned advantages over OMIP is the one published by Hessman et al in 2010 (68). In this randomised clinical trial which includes 143 patients allocated to either video-assisted parathyroidectomy(VAP) or OMIP, it was shown predominantly that OMIP has a much shorter operative time than VAP (60 vs 84 minutes respectively) (Fig. 31). Of note is the fact that the patients belonging to the VAP group underwent either MIVAP or VAPLA. Furthermore, it was shown that both groups had similar incision lengths, equal, low rates of post-operative discomfort and complications associated with the procedure and high rates of cosmetic satisfaction. Conversion rates and outcome of the operation in terms of patients' post-operative hypercalcaemic rates did not differ significantly between the two groups. Importantly, as outlined by Barczynski et al in their review (65), such findings that contradict their own may be explained by the mixed type of intervention in the VAP group in Hessman's review, which was either MIVAP according to the Miccoli technique, or VAPLA according to the Henry technique.



DISCUSSION

Primary hyperparathyroidism is the third most common endocrine disorder, affecting 1-3% of the population in the western world (4, 5), while being the commonest cause of hypercalcaemia (1). Its incidence peaks around the fourth and fifth decade, and women are more susceptible than men (2, 3). While patients used to present with a variety of clinical symptoms, summarised by the famous aphorism "stones, bones, groans and moans", nowadays, the majority of these patients are asymptomatic, with their diagnosis of pHPT being a random biochemical finding (4). If symptomatic, patients with pHPT may suffer from renal and ureteric calculi, bone disorders, such as osteitis fibrosa cystica and brown tumours, abdominal pain, constipation, neuropsychiatric conditions or even present with hypercalcaemic crisis (6-8). PHPT may be caused by a variety of pathological conditions, such as a solitary parathyroid adenoma, diffuse glandular hyperplasia (sporadic or in the context of MEN syndrome types 1 and 2A), multiple adenomas and parathyroid carcinoma.

Surgery is the only definitive therapeutic approach for pHPT (4). While open bilateral neck exploration has until today been the gold standard for treatment of this condition, the acknowledgement that pHPT is in >80% of cases caused by a single parathyroid adenoma has led to a continuous tendency towards the implementation of minimally invasive techniques (2, 16, 19). Indeed, in current practice for solitary parathyroid adenomas, endocrine surgeons prefer a focused approach that aims to remove the responsible hyperfunctioning gland, rather than explore all four glands, as was the norm with BNE.

In order for such an approach to be implemented, two significant prerequisites need to be met. Predominantly, since visualisation of all four glands is not the case with these minimally invasive techniques, adequate and reliable pre-operative localisation of the responsible gland needs to take place. Furthermore, a method is required that would enable the surgeon to intra-operatively ensure the successful outcome of the procedure, and eliminate the risk of leaving residual pathological tissue behind. As far as pre-operative localisation is concerned, modern imaging modalities are employed, such as cervical ultrasonography and 99-Technetium sestamibi scan, with high rates

of sensitivity and specificity (3), while their combination has been shown to be superior to each of them being used separately, with sensitivity reaching 96% (2). If these imaging modalities fail to show the hyperfunctioning parathyroid gland, 4D-CT, MRI or invasive methods may be employed (26, 28, 31). In terms of intra-operative confirmation of adequacy of excision, the most popular method is IOPTH measurement, and in particular, a >50% drop from the highest pre-incision or pre-excision PTH level ten minutes after removal of the gland (Miami criteria) (2, 4, 33). IOPTH measurement is known to change the surgical planning from MIP to BNE in 10% of patients (33), while there is evidence that it is beneficial not only in cases of discordant pre-operative localisation (35), but also for patients with concordant imaging (34), although controversy exists for the latter.

The availability of these two significant prerequisites has led to an outstanding evolution of MIP, with various techniques emerging, sharing many common features, while at the same time demonstrating subtle different characteristics, that render the choice of one over the other debatable. Indeed, since the first unilateral neck exploration by Tibblin in 1982, a number of modern techniques has been presented. Minimally invasive radio-guided parathyroidectomy (MIRP) by Norman and Cheda, video-assisted parathyroidectomy by the lateral approach (VAPLA) by Henry and endoscopic parathyroidectomy (EP) by Gagner are a few well-known techniques. Nevertheless, the most popular techniques are open minimally invasive parathyroidectomy (OMIP) and of course, minimally invasive video-assisted parathyroidectomy (MIVAP) by Miccoli.

In order for these modalities to be considered superior to BNE, it needs to be shown that they can rival its effectiveness and success rates in the management of pHPT. Indeed, it is true that the cure rate achieved by traditional BNE exceeds 95%, with a minor rate of complications, not exceeding 3% (16). Thus, MIP techniques must demonstrate that they are at least equally effective and safe as BNE, while at the same time providing additional benefits. Examples of such benefits include the cosmetic outcome, as well as the lesser degree of tissue dissection, which enables the surgeon to avoid damage to the remaining parathyroid glands and the RLN. Nevertheless, according to current guidelines, open BNE should be performed in cases of intra-operative failure of identification of the responsible gland, inadequate drop of IOPTH, discordant pre-operative localisation studies, multiglandular disease, suspected or known MEN syndrome (types 1 and 2A) or familial pHPT (2).

Given the relative novelty of such techniques, it is anticipated that the number of reviews in literature that aim to perform an evidence-based comparison between MIP and traditional open BNE is rather limited. This is also true for reviews that aim for a comparison among all minimally invasive modalities. Since MIVAP is undoubtedly one of the most popular minimally invasive techniques for parathyroidectomy, this systematic review aims to establish its advantages not only over BNE, but also over the remaining MIP techniques. In this way, its contribution to scientific knowledge on the optimal surgical approach for parathyroidectomy is profound.

It is also true that MIP is not currently indicated for familial hyperparathyroidism and multiglandular disease according to recent guidelines (2, 20). However, as minimally invasive techniques constantly evolve, and as MIVAP may also provide bilateral exploration of all four glands, it is of particular value to ascertain whether MIP might be employed for such conditions, thereby expanding existing indications. Furthermore, increasing numbers of minimally invasive parathyroidectomies are being performed under loco-regional anaesthesia, with profound benefits in terms of patient satisfaction and costs, and therefore, research on this issue will provide valuable knowledge with practical implications.

As far as MIVAP is concerned, patients with pHPT who are candidates to undertake the procedure range from 37% to 71% (16, 49, 69), while the conversion rate to open BNE also varies, and ranges from 0.9% to 8% in large series (49, 69). This discrepancy in patient conversion rates may be explained not only by intra-operative difficulty in identification of the hyperfunctioning gland, suspicion or presence of multiglandular disease or ectopic localisation of the gland, but also by the varying levels of surgical experience on the procedure and the criteria for patient selection. Many studies in literature suggest that MIVAP is associated with very high cure rates (reaching 98%), and minimal complication rates, which range from 2.7-4.4% for post-operative transient hypocalcaemia, and <1% for permanent RLN palsy (48-51). Levels of persistent hyperparathyroidism after MIVAP are very low (2.1%) (49).

The unique combination of a midline incision, which is much smaller than the one used for BNE (1.5-2cm), along with the insertion of an endoscope that provides magnification of underlying structures has rendered MIVAP one of the most popular techniques for MIP. These features together with the absence of trocars and the avoidance of gas insufflation provide additional appeal. The use of the 5mm endoscope magnifies structures, thus enabling the surgeon to identify the RLN and the parathyroid glands more easily. In addition, the central access that is used in this technique facilitates bilateral neck exploration, by means of rotation of the endoscope when required, for instance in cases of suspected multiglandular disease, inadequate or discordant pre-operative imaging studies and failure to trace the pathological gland during the operation (16). Furthermore, it may be performed in cases where IOPTH levels cannot be obtained. Indeed, video-assisted bilateral neck exploration has been proven to be equally safe and effective as MIVAP followed by IOPTH, with equal operative times (22).

Moreover, another advantage of MIVAP which is of crucial importance, is that it allows for treatment of concurrent thyroid pathology. Indeed, MIVAP may achieve thyroid lobectomy, or even total thyroidectomy through the same scar, without the need for conversion to open BNE, as would be the case with OMIP or any other endoscopic technique (39, 41, 49, 69). What is more, MIVAP is advantageous in that it may be used to explore deeply located inferior hyperfunctioning glands, such as retrosternal or intrathymic (16). This stems from the fact that the endoscope in MIVAP is not restricted by any trocar, and can therefore be rotated in any direction to

visualise the entire neck and upper mediastinum. Furthermore, this minimally invasive technique does not require neck hyperextension and minimises tissue dissection. These two features are significant contributing factors to the lower degree of post-operative pain which is associated with this procedure.

On the other hand, MIVAP is followed by a certain number of drawbacks. Concerns relating to cost and operative time are established in a considerable number of reviews attempting a comparison among existing techniques for parathyroidectomy and will be further analysed. However, one feature that needs to be stressed is that MIVAP requires the presence of two assistants, as one of them must hold the endoscope.

The advantages of MIP, and in particular MIVAP over traditional BNE for pHPT have been well-established in a significant number of reviews in literature. These involve randomised control trials, retrospective and prospective reviews, therefore providing adequate reliability and reproducibility of provided evidence. In most of these studies, a number of exclusion criteria was set (39, 42). These included large parathyroid glands >3cm in diameter, as it is more laborious to extract such glands through a small incision. Furthermore, preceding cervical operations also discouraged surgeons from attempting minimally invasive procedures. Moreover, family history of parathyroid disease, suspected multiglandular involvement and discordant or absent pre-operative localisation of the pathological gland dissuaded employment of MIP and resulted in BNE. In addition, suspicion for parathyroid carcinoma would lead to BNE, as it is very likely for extensive dissection and excision of tissues to be required, which would be hampered by small incisions and restricted manipulation. Finally, in many cases, concurrent thyroid pathology, such as a nodular goitre or inflammatory thyroid conditions do not constitute an indication for MIP. Nevetheless, as previously mentioned, a number of other studies have examined the use of MIVAP for simultaneous treatment of pHPT and thyroid pathology. In order to ascertain the value of MIVAP in modern surgical practice, several parameters have been assessed, which include not only cure rates and those of recurrent or persistent hyperparathyroidism, but also a wide spectrum of features, such as patient satisfaction, post-operative pain and analgesia requirements, length of hospital stay, conversion rates to open BNE, RLN palsy rates and levels of post-operative hypocalcaemia, operative time and cost.

To start with, the degree of post-operative pain has been unanimously agreed to be significantly reduced after MIVAP, compared to traditional cervicotomy. Indeed, this has been assessed in various studies by means of the Visual Analogue Scale (VAS) at different intervals after the operation, and on every occasion, patients seem to be benefitted from a minimally invasive approach (16, 39, 43, 45, 69). This reduction may be explained not only by the lesser degree of tissue dissection involved in minimally invasive surgery, but also by the avoidance of neck hyperextension during the procedure (39). A natural consequence of this is that patients required a smaller amount of post-operative analgesics.

Furthermore, the next striking benefit of MIVAP is the cosmetic outcome. It has been reported throughout the literature that this technique is associated with a higher level of patient satisfaction (16, 41, 43, 45, 49, 51, 69). More specifically, rates of patient satisfaction with the cosmetic result may exceed 90% both in the short term and also in the long run (49, 51). This is attributed to the shorter length of the incision, and characterises not only MIVAP but also the remaining MIP modalities, as better cosmesis is one of the foundations upon which minimally invasive surgery has been built. In terms of operative time, MIVAP again supersedes open BNE, as in the majority of studies, it is evidently shorter (16, 39, 41, 45), ranging from 29 to 78 minutes. This stems from the fact that MIVAP is a targeted approach to an already recognised pathological gland and does not require visualisation of the remaining glands, as is the norm with BNE, thus saving valuable operative time.

Similarly, MIVAP has been associated with a reduced length of hospital stay (40, 41, 43). This may be explained not only by the reduced level of post-operative pain and analgesia requirement, but also by the lesser degree of tissue dissection and damage which hinders the need for a drain placement, that would prolong patient recovery. Moreover, MIVAP may be performed even under loco-regional anaesthesia, which evidently allows for a more rapid patient discharge (16).

However, as previously mentioned, the milestone that MIVAP had to reach predominantly, was to prove that it is at least equally effective as BNE for biochemical cure of the parathyroid state. Several studies indicate that this is actually true (38, 45-47), while others, for instance a retrospective review by Udelsman et al, have shown that cure rates are even higher than those achieved by BNE (40), reaching 99.4%. Such excellent cure rates may be explained by the combination of appropriate patient selection, reliable pre-operative localisation of the pathological gland, IOPTH measurement, and the ability to perform video-assisted BNE in cases of failed intra-operative identification of the gland or if a suspicion of multiglandular disease has been raised (39). Indeed, rates of both persistent and recurrent hyperparathyroidism are kept to a minimum and in comparable levels to those after BNE, while MIVAP has additionally been used for re-exploration after failure of post-operative calcium level normalisation (46).

As far as complications are concerned, it has been shown that they do not exceed the rates of traditional cervicotomy, and this is reflected in the majority of reviews (39, 43, 44, 46, 47, 69). The complications that are the most severe after parathyroidectomy for treatment of pHPT and that have been particularly investigated in all the aforementioned reviews are post-operative hypocalcaemia and damage to the RLN, which may be either transient or permanent. As it has already been stated, BNE involved exploration and visualisation of all four parathyroid glands in order to recognise and excise the pathological tissue, however this inflicted in certain cases an inadvertent injury to the remaining parathyroid glands and even to one or both RLNs. On the other hand, MIP techniques involve a targeted, focused approach to find the responsible hyperfunctioning gland, which has already been identified on pre-

operative imaging, and thus practically eliminate the risk of bilateral RLN injury or permanent hypoparathyroidism. Nevertheless, the shorter length of the incision and the narrower operative field are associated in some cases (for instance in OMIP) with poorer visualisation of the related structures. Of course, this drawback does not apply for modalities that provide magnification of the anatomical structures by means of video-assistance, among which MIVAP is the best example. What is more, the assistant has to apply greater traction force to the retractors due to the smaller length of the incision and this sometimes accounts for accidental injury to the RLN.

The rates of post-operative transient hypocalcaemia range from 2.7% to 4.4% in most studies, while permanent RLN palsy was inflicted in less than 1% of cases (48-51). Such results are comparable to those after open BNE. What is more, Udelsman et al (40) found that complications were actually fewer in their study (1.45% versus 3.10% after BNE). This was subsequently confirmed in another study by Norman et al (41).

As stated previously, the conversion rate of MIVAP to open BNE ranges from 0.9% to 8% (49, 69), and it may even reach 14% (42, 44). Reasons that dictated conversion were missed adenomas, inadequate drop of IOPTH levels that was associated with multiglandular disease, false negative IOPTH, difficult dissection of tissues and failure of pre-operative localisation of the pathological gland (42). Additional causes that led to conversion were the presence of very small adenomas as well as large and friable adenomas that were difficult to be excised (44).

In the first years following the appearance of MIVAP and its gradual establishment in the management of pHPT, it was considered that it would augment costs, as it requires specific instrumentation (endoscope, video, light source, camera, small special instruments) (16). Nevertheless, it is a fact that nowadays, nearly all operating rooms have the aforementioned equipment. This in conjunction with the fact that small special instruments required for MIVAP are re-usable, explains why cost associated with the procedure has been significantly reduced. Indeed, in certain reviews, it has been found that MIVAP is actually correlated with reduced total costs compared to BNE (40).

Throughout this systematic review, an aspect of MIVAP that has been particularly highlighted is its unique ability to perform video-assisted bilateral neck exploration, thus combining the advantages of traditional cervicotomy with the benefits that encompass minimally invasive surgery. For this reason, a number of reviews attempted to clarify whether video-assisted BNE by MIVAP was equally effective as traditional, open BNE (46, 47). It was found that the former is as safe and effective as open BNE, and was successful in 97% of cases (46). Without prolonging operative time, it assured biochemical cure in 98.5% of patients, with minimal complication rates. In addition, rates of conversion to open BNE and persistent or recurrent hyperparathyroidism were minimal. Such findings are indeed very important, as they allow MIVAP to be used in cases of discordant or absent pre-operative localisation studies, and indeed, where IOPTH measurement is not available (39, 46, 47).

Furthermore, failure to recognise the pathological gland intra-operatively, as well as an inadequate drop in IOPTH may not necessarily require conversion to an open procedure, due to this unique feature of MIVAP, which distinguishes it from all other minimally invasive techniques for parathyroidectomy. Of course, to date, MIVAP is only indicated for cases of well-localised, solitary parathyroid adenomas, but such findings may change current guidelines towards a minimally invasive approach even for the aforementioned scenarios.

Similar findings apply for all remaining MIP techniques, proving that they demonstrate significant advantages over BNE when used for selected cases. To start with, OMIP, which is the most popular technique for MIP along with MIVAP, has been proven to be equally effective as open BNE for the management of pHPT (15, 61-64). More specifically, the two methods have no difference whatsoever in terms of biochemical cure rates, levels of persistent pHPT and complications. In addition, OMIP is superior to BNE in terms of operative time, length of hospital stay, costs and patient comfort (63, 64) and conversion is seldom required, thus constituting an excellent alternative provided that it is employed for cases where it is indicated (ie for solitary adenomas and not where suspicion of multiglandular disease or MEN syndrome has been raised).

VAPLA is another minimally invasive technique that has been shown to resemble BNE in terms of safety and effectiveness, especially for well-localised solitary adenomas that are small or deeply located in the cervix (18, 54). In addition, this technique is deemed suitable for adenomas located in the upper and posterior mediastinum (54). While complications are rare and comparable to open cervicotomy, the conversion rate is higher than that of MIVAP, and may reach 15.6%, as it is impossible to perform bilateral exploration of the neck by this technique (18). Due to this reason, concurrent thyroid pathology and suspicion of multiglandular disease constitute absolute contraindications for VAPLA.

Likewise, MIRP has been proven to share equal cure and complication rates as conventional parathyroidectomy (13) while superseding it in terms of operative time and costs. The technique involves a hand-held gamma probe, which identifies the pathological gland and subsequently confirms successful excision, thus eliminating the need for IOPTH measurement (55). Furthermore, it is easily performed under loco-regional anaesthesia, and thus allows for early discharge from hospital. Indeed, as many as 65% of patients undergoing MIRP may be discharged within the first five hours following the procedure (13). Naturally, MIRP is associated with all the advantages of minimally invasive surgery, and is additionally considered advantageous for cases of previous thyroid or parathyroid surgery (41).

As far as total endoscopic parathyroidectomy (EP) is concerned, it provides higher rates of patient satisfaction compared to open BNE and exceptional cosmetic results, while minimising post-operative pain (57, 58). At the same time, it is not associated with a higher rate of complications and provides equally satisfying cure rates as BNE.

Moreover, it does not prolong the duration of hospital stay. Multiglandular disease or negative exploration of the cervix would warrant conversion to conventional, open parathyroidectomy, as is the case in up to 15% of these patients (58). Furthermore, EP has shown similar results regardless of whether it is performed by gas insufflation or by a gasless, skin-lifting approach (59, 70). In addition, it has been attempted to perform EP by means of various extra-cervical approaches, from the chest wall, the axilla, or indeed the breast. Such approaches are associated with a flawless cosmetic outcome, but on the other hand, with a significantly greater degree of invasiveness and complications (19).

The second target of this systematic review is to perform an objective comparison among all minimally invasive techniques for parathyroidectomy, and attempt to ascertain whether MIVAP supersedes the rest for the treatment of pHPT. In global literature, two randomised clinical trials, one by Barczynski et al (65) and one by Hessman et al (68) are the most popular studies on this issue, followed by a number of smaller reviews and case-control studies. The majority of these aim to compare MIVAP and OMIP, as these are the two most popular techniques for MIP.

Importantly, both MIVAP and OMIP were proven to be equal in terms of biochemical cure rates (5, 65-68). Furthermore, no major difference was traced between these two techniques in terms of complications (65-68). More specifically, as far as damage to the RLN is concerned, it was demonstrated that although MIVAP allows for more reliable visualisation of the RLN (in up to 92.7% of cases), as it magnifies anatomical structures up to ten times, the rate of damage to the nerve was equally low for both techniques (66). Moreover, the length of hospital stay was generally found to be the same for both techniques (65, 66), while in a review by Melck et al it was demonstrated that video-assisted parathyroidectomy may be correlated with earlier patient discharge (67). Additionally, conversion rates to traditional parathyroidectomy vary, with some reviews demonstrating similarity (65, 68), while others show a considerable discrepancy (10% for OMIP versus 1.9% for MIVAP) (5). However, conversion rates for MIVAP have reportedly reached 14% in other cases (67).

Undoubtedly, MIVAP is associated with a significant number of advantages over OMIP, as demonstrated in the vast majority of studies contemplating this issue. The biggest number of such studies come to the conclusion that MIVAP is associated with significantly reduced post-operative pain both within the first hours following the procedure as well as in the longer run (65, 66). This was assessed by means of the visual analogue scale (VAS), and pain intensity was reduced by 32.7% twenty-four hours following MIVAP (65). Nevertheless, this advantage of MIVAP was not found by Hessman et al in their randomised control study, which showed that post-operative discomfort was similar following both techniques (68). A profound consequence of this benefit is the smaller quantity of analgesics needed by the patients post-operatively, and therefore a decrease in request rates for analgesia (65, 66), which was stressed by all reviews apart from one (67). Another advantage of MIVAP over OMIP is the superior cosmetic outcome due to the smaller length of scars (17.8mm on

average versus 41.4 mm respectively) (65-67). What is more, patients having undergone MIVAP had greater rates of satisfaction post-operatively, not only in the immediate aftermath, but also six months following parathyroidectomy (65, 66). In addition to these findings, Barczynski et al also demonstrated a significant amelioration of the quality of life after MIVAP, concerning physical functioning and bodily pain, as assessed by the SF-36 questionnaire (65). On the other hand, Hessman et al failed to identify the aforementioned advantages in their study, concluding that the two techniques share similar incision lengths and rates of patient satisfaction (68).

As far as operative time is concerned, the existing reviews in literature display contradicting evidence. Some of them, like the initial randomised clinical trial by Barczynski et al, have found that no crucial difference exists in operative time between the two methods (65, 67). Nonetheless, eight years later, the same author concludes that MIVAP is actually associated with longer operative time than OMIP (42.5 versus 37.4 minutes), and this is confirmed by Hessman's trial as well (67). It is also true that nearly all published studies agree that MIVAP is associated with significantly higher costs than OMIP. This was mainly due to additional costs correlated with the endoscopic equipment required for MIVAP (5, 65, 66). Another contributing factor to this is the relatively longer operative time, which may in some cases render MIVAP 25% more expensive than OMIP (66). However, Melfa et al point out three factors that ought to be considered (5). Indeed, MIVAP may be performed under loco-regional anaesthesia, thus eliminating the cost associated with general anaesthesia (5, 21). Furthermore, it may be employed for cases of discordant or non-diagnostic pre-operative imaging due to its ability to perform bilateral neck exploration, and thus costs associated with the need for two concordant imaging modalities (as was the case in their study) will be greatly diminished. In addition to these, MIVAP, unlike OMIP, may be used for treatment of simultaneous thyroid pathology, avoiding the need for conversion to an open procedure in a significant number of cases. All these features in conjunction with the fact that endoscopic equipment is nowadays largely available in every operating theatre imply that future research should re-address the issue of cost-effectiveness for these procedures.

Overall, the majority of existing studies agree that these two techniques display similar cure rates and complications, and thus constitute a safe and reliable approach for the management of pHPT. MIVAP appears to be associated with reduced post-operative pain and analgesia requirements, as well as better cosmetic results, smaller incisions and higher rates of patient satisfaction. On the other hand, it appears to be more expensive than OMIP, whereas operative time, although the results are relatively conflicting, seems to be longer with MIVAP. As previously mentioned, the findings of Hessman et al (68) were contradictory to those of the remaining studies on this issue, and that could be attributed to the mixed type of video-assisted intervention in their study, which was either MIVAP or VAPLA (66). Other studies, like the one by Barczynski et al in 2014 (66) were biased from the point of view of allocation to either method, as this relied on patients' preference, although the authors mention that

this has not interfered with the credibility of the study. It is also stressed that adequate surgical experience in open BNE and endoscopic surgery is an indispensable predisposition for the high cure rates obtained by MIVAP (66). Furthermore, another significant point is that although no such indication exists formally, MIVAP should be preferred over OMIP for deeply sited or posteriorly located adenomas, in order to avoid excessive traction that might injure the RLN (5).

A comparison of MIVAP with the other minimally invasive techniques for parathyroidectomy is also of great value and importance. Interestingly, VAPLA is associated with a higher rate of contraindications than MIVAP (43% versus 29%), and that can be attributed to the ability of the latter to perform bilateral neck exploration, allowing its use in cases of discordant findings on pre-operative imaging, as well as treatment of concurrent thyroid pathology (16, 54). This fact could also explain the slightly higher rate of conversion to traditional parathyroidectomy with VAPLA. Nevertheless, VAPLA is equally safe and effective, and may offer an advantage in cases of small,solitary adenomas that are found deeply in the cervix or in the upper and posterior mediastinum, usually arising from the superior parathyroid glands (18, 54).

When it comes to MIRP, it is well known that due to the use of a hand-held gamma probe, which identifies the pathological gland, it allows for avoidance of IOPTH measurement and a subsequent reduction in operative time and costs in comparison with traditional parathyroidectomy (13, 55). In addition, it may easily be performed under loco-regional anaesthesia, while providing a benefit for patients having undergone previous thyroid or parathyroid operations (41). Nevertheless, it has been shown that the gamma probe is not always reliable for the identification of the hyperfunctioning parathyroid gland. Indeed, it correctly localised 66% of adenomas in a review (56), while the level of intra-operative confirmation of cure reached 84%. In contrast, IOPTH was successful in 98% of cases (ie demonstrated adequate reduction according to Miami criteria). Hence, IOPTH was regarded as a more reliable tool for accurate prediction of the success of the operation, compared to the gamma probe and MIRP.

Total endoscopic parathyroidectomy (EP) has proven its excellent cosmetic results (57), which rival these of the remaining minimally invasive techniques. However, as a rule, it is not suitable for bilateral exploration of the neck, contrary to MIVAP, although some studies report successful totally endoscopic BNE in experienced hands (58). Thus, MIVAP has a potential advantage over EP from that perspective.

The properties of MIVAP, and especially its ability to perform video-assisted BNE has motivated surgeons worldwide to search for expansion of its indications in the management of the parathyroid state. Indeed, even though current guidelines suggest that minimally invasive techniques should be used strictly for cases of a solitary, well-localised adenoma, a number of studies attempt to identify the potential benefits of MIVAP for familial hyperparathyroidism, or even secondary hyperparathyroidism

and parathyroid carcinomas (20, 52, 53).The rationale is that video-assisted BNE performed by MIVAP allows the surgeon to reliably explore the entirety of the cervix, and thus identify any abnormal parathyroid tissue, regardless of whether the pre-operative localization studies were concordant or not, essentially mimicking traditional cervicotomy. Consequently, it was shown that MIVAP may successfully perform subtotal parathyroidectomy for cases of familial and secondary hyperparathyroidism in some occasions. Furthermore, it was reportedly used for treatment of a patient with a suspected parathyroid carcinoma, along with the performance of en block thyroid lobectomy. Such findings will undoubtedly aid in shaping the future of parathyroid surgery and will generate the motivation for further research.

Additionally, costs associated with MIVAP may be further reduced by implementation of regional anaesthesia, as it has been demonstrated that the latter is safe and also correlated with diminished operative time and post-operative pain (21). This along with the unique qualities and outcomes of MIVAP, not only in terms of cosmetic outcome and patient satisfaction, but also its ability to carry out video-assisted BNE and management of simultaneous thyroid pathology, have made it one of the most appealing techniques for parathyroidectomy. Indeed, it has established its place for the treatment of solitary parathyroid adenomas that have been well localised pre-operatively, changing surgeons' preference in latest years from the traditional gold standard of open BNE to a minimally invasive approach. Furthermore, from what has been concluded in the aforementioned studies, it is evident that MIVAP possesses special properties that distinguish it from the remaining MIP techniques, even OMIP, which together with MIVAP is currently the most popular minimally invasive modality. Emerging studies are steadily being published that demonstrate a tendency towards a reduction in costs associated with this procedure, that consists its main drawback. Such studies, in conjunction with others that show a potential for gradual expansion of its indications, including cases of familial or secondary hyperparathyroidism, multiglandular disease or even parathyroid carcinoma, solidify the view that the place of MIVAP in Endocrine Surgery will greatly evolve in the near future, potentially making it the cornerstone in the management of pHPT.

CONCLUSIONS AND RECOMMENDATIONS

Primary hyperparathyroidism is a common endocrinopathy affecting calcium homeostasis (4, 5). Until very recently, the gold standard in the treatment of this condition has been open bilateral exploration of the neck. Nowadays, with the evolution of minimally invasive surgery, new techniques arise that promise better cosmetic results, greater patient satisfaction, reduced post-operative pain and shorter hospital stay, while achieving equal success rates and sharing similar complications with their traditional predecessor. Among these, MIVAP has a central role, and a number of reviews in global literature provide evidence to support it. Nevertheless, no review exists in literature that performs not only a comparison of MIVAP with traditional parathyroidectomy, but also an evidence-based comparison of all

minimally invasive techniques at the same time. The primary goal of this study was to bridge this gap, therefore attempting a systematic review of existing literature with a view to answering two fundamental questions: whether MIVAP supersedes traditional, open BNE for the management of pHPT, and subsequently whether it is superior to other MIP techniques.

It is important to bear in mind that current guidelines suggest that minimally invasive parathyroidectomy is indicated only for cases of a solitary parathyroid adenoma, well-localised in pre-operative imaging. As a matter of fact, solitary adenomas account for >80% of cases of pHPT, which allowed MIP to flourish (2, 16, 19). Indeed, modern imaging modalities provide reliable localization of the hyperfunctioning parathyroid gland(s) (ultrasonography, sestamibi, 4D-CT, MRI). This, along with the implementation of intra-operative PTH measurement shortly after excision and removal of the pathological gland, thus confirming successful operative outcome and total removal of the pathological tissue, are the milestones upon which MIVAP has been built (2, 4, 33).

MIVAP achieves exceptionally high cure rates (up to 99.4%), similar to those achieved by open BNE, or even higher, while keeping the rate of complications to a minimum (2.7-4.4% for transient hypocalcaemia and <1% for permanent RLN palsy) (48-51). At the same time, it involves minimal rates of persistent hyperparathyroidism, while it requires conversion to an open procedure in 0.9% to 8% of cases (49, 69). Furthermore, its ability to perform video-assisted bilateral exploration of the neck, through a small midline incision, the magnification it provides for subtle anatomical structures, such as the RLN and the parathyroid glands, and also its allowance for simultaneous treatment of thyroid pathology constitute the main advantages of MIVAP that differentiate it from all others (22, 39, 41, 49, 69). In particular, it has been demonstrated that video-assisted BNE performed by MIVAP is equally safe and effective as open BNE, guaranteeing biochemical cure in 98.5% of cases (46). On the other hand, costs and operative time appear to be the main drawbacks of the procedure.

The advantages of MIVAP over open BNE have been demonstrated in a number of reviews in literature, with varying degrees of reliability, ranging from case reports, prospective and retrospective studies, and reaching randomised control trials. The former has consistently been associated with reduced post-operative pain and analgesia requirements, as well as superior cosmetic outcome, with smaller incisions and increased patient satisfaction (16, 39, 41, 43, 45, 49, 51, 69). Moreover, it allows for shorter hospital stay and reduced operative time. As far as cost is concerned, although it is a recognised disadvantage of MIVAP particularly due to special equipment and instrumentation, it has been considerably reduced in recent years and a number of reviews have found that it is actually less than that of open BNE (40).

In addition to MIVAP, all minimally invasive techniques for parathyroidectomy have proven their benefit over open BNE, for selected cases of pHPT. OMIP is as safe and

effective as BNE (15, 61-64), while superseding it in terms of operative time, length of hospital stay, costs and patient comfort. The same applies for MIRP, which allows for a more rapid discharge, providing an additional advantage for cases of previous thyroid or parathyroid surgery (41). What is more, VAPLA is ideal for well-localised, small or deeply located solitary adenomas, and those situated in the upper and posterior mediastinum (54), while being contraindicated for cases of simultaneous thyroid pathology and multiglandular disease, due to its inability to perform bilateral neck exploration. Moreover, EP shares similar advantages, and may be performed by gas insufflation or by a skin-lifting technique. Further to this, several extra-cervical approaches exist (from the chest wall, the axilla and the breast) which provide perfect cosmesis but also a greater number of complications (16).

With regards to the second goal of this systematic review, which is a comparison among MIP techniques, data from various studies, and indeed two randomised control studies, provide interesting evidence on this issue. Comparing MIVAP with OMIP, these two techniques are equal in terms of biochemical cure rates, number of complications (65-68), length of hospital stay and conversion rates to traditional parathyroidectomy (although a few studies demonstrate considerably reduced conversion rates with MIVAP). Nevertheless, there is undoubtable superiority of MIVAP when it comes to post-operative pain, and analgesia requirements, with pain intensity being reduced by 32.7% following MIVAP (65, 66). Furthermore, MIVAP supersedes in that it guarantees a better cosmetic result, with minimal length of incision (65-67), thus increasing patient satisfaction and post-operative quality of life. Moreover, it should be selected over OMIP for deeply sited or posteriorly located adenomas (5).

However, there is conflicting data on operative time, with most studies concluding that MIVAP is actually associated with a prolongation of operative time and increased cost (up to 25% more expensive) when compared with OMIP (68). It is a fact though, that a reduction of cost associated with MIVAP has been achieved in later years, due to the availability of endoscopic equipment in most operating theatres, and further studies need to assess this. In addition, MIVAP displays a range of significant advantages, such as bilateral exploration of the neck, which could in some cases render the requirement for two pre-operative localization studies unnecessary, thus reducing cost (5). Furthermore, it allows for treatment of concurrent thyroid pathology, hence reducing the necessity for conversion to an open procedure in these cases. Overall, cost-effectiveness of this technique is a field that needs to be re-assessed.

Comparing MIVAP with VAPLA, it was shown that the latter is associated with a greater number of contraindications and mildly elevated conversion rates (16, 54), as it cannot perform bilateral exploration of the neck. In addition, when it comes to MIRP, the use of a hand-held gamma probe instead of IOPTH measurement was demonstrated to be less reliable than the latter for successful prediction of the operative outcome (56). It is, however, preferred for cases having had previous

cervicotomy, and also allows for reduced operative time and costs. Moreover, EP is usually not suitable for endoscopic BNE, as opposed to MIVAP, and hence the latter may be considered advantageous.

In addition to these, due to the opportunity MIVAP provides for video-assisted BNE, it has been used for cases of familial and secondary hyperparathyroidism, and even for cases of suspected parathyroid carcinomas (20, 52, 53) with successful performance of subtotal parathyroidectomy in selected cases. Furthermore, it is now well known that MIVAP may be performed under regional anaesthesia, thus reducing costs associated with the procedure, as well as the degree of post-operative time and pain (21).

Overall, the current systematic review, after taking into consideration a significant number of studies from the global literature, has demonstrated that MIVAP is superior to open BNE and also the remaining minimally invasive techniques for the management of selected cases of pHPT, as outlined in the latest guidelines (2). This stems from the fact that it not only guarantees similar cure and complication rates, but that it also shows significant advantages in cosmesis, post-operative pain, patient satisfaction and length of hospital stay. In particular, MIVAP shares all the benefits of a minimally invasive procedure, while at the same time providing unique advantages, such as bilateral exploration of the neck and treatment of concurrent thyroid pathology. Accurate pre-operative localization of the pathological hyperfunctioning gland is advisable, although this technique could be considered for cases of negative or discordant imaging, as it allows for BNE (5). In addition, most studies conclude that IOPTH measurement increases the credibility of MIVAP (34, 35), and is more reliable than the gamma probe used in MIRP (56).

All the above justify the fact that MIVAP has greatly contributed to a gradual shift from open BNE, as the gold standard for management of pHPT, to a less invasive approach. Furthermore, being the most popular MIP technique along with OMIP, it was demonstrated in this systematic review that MIVAP encompasses a number of advantages over the latter. Naturally, in certain aspects like cost and operative time, OMIP has in most cases been shown to be superior, but recent studies aim to contradict this conclusion. Bearing this in mind, it is evident why the special advantages of MIVAP have motivated a continuously increasing number of endocrine surgeons to adopt this technique for the treatment of pHPT.

In conclusion, the present review recommends MIVAP as the procedure of choice for cases of solitary, well localised parathyroid adenomas. As previously mentioned, minimally invasive parathyroidectomy is a relatively new field of research, and the number of existing studies on this issue, especially those contemplating a comparison among minimally invasive procedures is limited. Furthermore, some of them are biased by the fact that the patients selected which procedure they would undergo for the treatment of their condition, and so lacked randomisation. Hence, it is obvious that a bigger number of studies, and especially randomised control trials is required, for

further evaluation and potential confirmation of the aforementioned data. Such studies should particularly aim for a comparison of MIVAP with all other MIP techniques, as there are currently only two randomised control trials on this issue. As MIVAP is used in increasing frequency by many surgeons worldwide, available data for such studies will soon be available.

In addition, as demonstrated before, MIVAP may have an important role in the management of other types of pHPT, such as familial or pHPT associated with MEN type 1 and 2A syndromes. In other words, the role of MIVAP in cases that may involve multiglandular disease needs to be further ascertained by future studies, thus potentially changing current guidelines in order to incorporate such cases. The same applies for cases of negative or discordant pre-operative imaging findings, as video-assisted exploration of the neck performed by MIVAP could aid in the intra-operative identification of all pathological tissue. The inclusion of such cases in the indications for MIVAP could lead to it being used for increased numbers of patients, covering the whole spectrum of pHPT. What is more, an expansion of its indications with a simultaneous reduction in cost associated with the procedure, will establish the position of MIVAP as the treatment of choice for a variety of patients with pHPT.

The same applies for patients requiring simultaneous treatment of thyroid pathology. Several studies have proven that MIVAP may successfully perform lobectomy or even total thyroidectomy. In addition, it has been used for the treatment of a patient with parathyroid carcinoma, which involved en block thyroid lobectomy (53). Bearing in mind that presence of concurrent thyroid disease has thus far been considered one of MIP's major contraindications, it is obvious that the confirmation of such findings by newer studies and thorough research will further increase the spectrum of MIVAP's indications. Furthermore, the fact that it may easily be performed under loco-regional anaesthesia (21) implies that MIVAP may be used for patients with significant co-morbidities, who do not constitute ideal surgical candidates, and would most likely not be able to undergo a procedure under general anaesthesia, such as traditional open BNE. Such a perspective has profound benefits for these groups of patients and provides them with an opportunity for definitive treatment of their condition.

In conclusion, despite further studies and research being required for confirmation of the aforementioned findings and expansion of the technique's range of indications, it is evident that MIVAP is currently the most advantageous and promising minimally invasive modality for treatment of selected cases of pHPT. Its unique features have the ability to render this technique the new gold standard for the treatment of this common endocrine disorder within the following years. By performing a detailed comparison of MIVAP with traditional parathyroidectomy and other minimally invasive techniques at the same time, which has so far been absent from existing literature, this systematic review constitutes an important foundation for the evolution of the technique's role in current surgical practice and its implementation by an increasing number of endocrine surgeons in the years to come.

ABSTRACT

BACKGROUND: Open bilateral neck exploration (BNE) has until recently been the gold standard for the surgical treatment of primary hyperparathyroidism (pHPT). Lately, a shift towards minimally invasive parathyroidectomy has occurred. The aim of this systematic review is to compare minimally invasive video-assisted parathyroidectomy (MIVAP) with traditional BNE and the remaining minimally invasive techniques, confirm its indications, advantages and drawbacks, and seek for potential expansion of its current indications.

MATERIAL AND METHODS: Data from randomised control trials, prospective and retrospective reviews, as well as other studies, were collected from Pubmed. Fourteen studies contemplated a direct comparison of MIVAP with open BNE, while 8 others compared the former with other minimally invasive techniques, especially open minimally invasive parathyroidectomy (OMIP). Additional information was collected from other reviews regarding anaesthetic implications and further potential indications for MIVAP. Recognition of bias in these studies was achieved and mentioned where appropriate. The main outcomes on which this comparison has been founded were safety, effectiveness, cosmesis, post-operative pain, length of hospital stay, operative time and cost.

RESULTS: MIVAP has consistently demonstrated equal cure rates (up to 98%) as open BNE, with similar numbers of complications, ranging from 2.7-7.7% for transient hypocalcaemia and <1% for permanent RLN palsy. It shows superiority in terms of cosmetic outcome, with smaller incisions (1.5-2cm) and greater patient satisfaction (approaching 90%) in the short and long term. Furthermore, MIVAP is associated with reduced post-operative pain and analgesia requirements, diminished length of hospital stay and operative time, better visualisation of the RLN, in addition to providing the opportunity for video-assisted BNE and treatment of concurrent thyroid pathology. Conversion rates range from 0.9% to 8% in most studies. Nevertheless, MIVAP is more expensive than BNE, however the cost-effectiveness of the procedure is continuously being improved. The same advantages apply when comparing MIVAP to OMIP, with the exception of operative time and cost, where the latter supersedes (25% less expensive than MIVAP). It is also ideal for posteriorly or deeply located adenomas. MIVAP is also more reliable than the gamma probe used in minimally invasive radio-guided parathyroidectomy (MIRP), has fewer contraindications than video-assisted parathyroidectomy by the lateral approach (VAPLA) and endoscopic parathyroidectomy (EP), and may be considered for cases of multiglandular disease, familial and secondary hyperparathyroidism, due to its ability to perform video-assisted BNE.

CONCLUSIONS: MIVAP is superior to open BNE for the treatment of selected cases of pHPT (solitary, well-localised parathyroid adenomas), as it not only is similarly

safe and effective as the latter, but also displays significant advantages in terms of cosmesis, post-operative pain and patient satisfaction. In addition, it is preferred to other minimally invasive techniques, as it allows for video-assisted BNE and simultaneous treatment of thyroid disease. Associated cost is an issue but this is constantly being improved. An expansion of the existing spectrum of indications for MIVAP is being attempted, for treatment of multiglandular disease, familial and secondary hyperparathyroidism, with encouraging results, motivating future research in this technique's role for the surgical managment of this common endocrinopathy.

ΠΕΡΙΛΗΨΗ

ΥΠΟΒΑΘΡΟ: Η ανοικτή αμφοτερόπλευρη διερεύνηση του τραχήλου (BNE), υπήρξε ως πρόσφατα η επέμβαση εκλογής για τη χειρουργική θεραπεία του πρωτοπαθούς υπερπαραθυρεοειδισμού (pHPT). Τελευταία, μια στροφή προς την ελάχιστα επεμβατική παραθυρεοειδεκτομή έχει επισυμβεί. Ο σκοπός αυτής της συστηματικής ανασκόπησης είναι να συγκρίνει την ελάχιστα επεμβατική βίντεο-υποβοηθούμενη παραθυρεοειδεκτομή (MIVAP) με την παραδοσιακή BNE και τις υπόλοιπες ελάχιστα επεμβατικές τεχνικές, να επιβεβαιώσει τις ενδείξεις, τα πλεονεκτήματα και μειονεκτήματά της, και να αναζητήσει πιθανή επέκταση των υπαρχουσών ενδείξεών της.

ΥΛΙΚΟ ΚΑΙ ΜΕΘΟΔΟΣ: Δεδομένα από τυχαιοποιημένες κλινικές δοκιμές, προοπτικές και αναδρομικές ανασκοπήσεις, καθώς και άλλες μελέτες συνελέγησαν από τη βάση Pubmed. Δεκατέσσερις μελέτες πραγματεύθηκαν μια άμεση σύγκριση της MIVAP με την ανοικτή BNE, ενώ 8 άλλες συνέκριναν την πρώτη με άλλες ελάχιστα επεμβατικές τεχνικές, ιδιαίτερα την ανοικτή ελάχιστα επεμβατική παραθυρεοειδεκτομή (OMIP). Επιπρόσθετες πληροφορίες συνελέγησαν από άλλες μελέτες και αφορούσαν προεκτάσεις ως προς την αναισθησία και επιπλέον πιθανές ενδείξεις για την MIVAP. Η αναγνώριση των σφαλμάτων σε αυτές τις μελέτες κατέστη δυνατή και αναφέρθηκε όπου ήταν απαραίτητο. Τα κύρια αποτελέσματα στα οποία η σύγκριση αυτή βασίσθηκε ήταν η ασφάλεια, η αποτελεσματικότητα, το κοσμητικό αποτέλεσμα, ο μετεγχειρητικός πόνος, η διάρκεια της νοσηλείας στο νοσοκομείο, ο εγχειρητικός χρόνος και το κόστος.

ΑΠΟΤΕΛΕΣΜΑΤΑ: Η MIVAP έχει σταθερά επιδείξει ίδια ποσοστά ίασης (ως και 98%) με την ανοικτή BNE, με παρόμοιους αριθμούς επιπλοκών, που κυμαίνονται από 2,7% ως 7,7% για παροδική υπασβεστιαιμία και <1% για μόνιμη πάρεση του παλίνδρομου λαρυγγικού νεύρου. Επιδεικνύει υπεροχή όσον αφορά το κοσμητικό αποτέλεσμα, με μικρότερες τομές (1,5-2 εκ.) και μεγαλύτερη ικανοποίηση των ασθενών (που προσεγγίζει το 90%) βραχυπρόθεσμα και μακροπρόθεσμα. Επιπρόσθετα, η MIVAP συνδέεται με μειωμένο μετεγχειρητικό πόνο και απαιτήσεις σε αναλγησία, μειωμένη διάρκεια νοσηλείας στο νοσοκομείο και εγχειρητικό χρόνο, καλύτερη αναγνώριση του παλίνδρομου λαρυγγικού νεύρου, και επίσης προσφέρει τη δυνατότητα για βίντεο-υποβοηθούμενη αμφοτερόπλευρη διερεύνηση του τραχήλου (BNE) και θεραπεία σύγχρονης παθολογίας του θυρεοειδούς αδένα. Τα ποσοστά μετατροπής κυμαίνονται από 0,9% ως 8% στις περισσότερες μελέτες. Εν τούτοις, η MIVAP είναι πιο ακριβή από την BNE, παρόλα αυτά η σχέση κόστους-αποτελεσματικότητας της τεχνικής συνεχώς βελτιώνεται. Τα ίδια πλεονεκτήματα ισχύουν όταν συγκρίνεται η MIVAP με την OMIP, με εξαίρεση τον εγχειρητικό χρόνο και το κόστος, όπου η τελευταία πλεονεκτεί (25% λιγότερο ακριβή από την MIVAP). Είναι επίσης ιδανική για αδενώματα που εντοπίζονται σε οπίσθιο ή εν τω βάθει πλάνο. Επίσης, η MIVAP είναι περισσότερο αξιόπιστη από την γάμμα κεφαλή

(gamma probe) που χρησιμοποιείται στην ελάχιστα επεμβατική ραδιο-υποβοηθούμενη παραθυρεοειδεκτομή (MIRP), έχει λιγότερες αντενδείξεις από την βίντεο-υποβοηθούμενη παραθυρεοειδεκτομή μέσω πλάγιας προσπέλασης (VAPLA) και την ενδοσκοπική παραθυρεοειδεκτομή (EP), και δύναται να χρησιμοποιηθεί σε περιπτώσεις πολυαδενικής νόσου, οικογενούς και δευτεροπαθούς υπερπαραθυρεοειδισμού, λόγω της ικανότητάς της για διενέργεια βίντεο-υποβοηθούμενης BNE.

ΣΥΜΠΕΡΑΣΜΑΤΑ: Η MIVAP είναι ανώτερη της ανοικτής BNE για τη θεραπεία επιλεγμένων περιπτώσεων πρωτοπαθούς υπερπαραθυρεοειδισμού (μονήρη, καλώς εντοπισμένα αδενώματα παραθυρεοειδών), καθώς όχι μόνο είναι εξίσου ασφαλής και αποτελεσματική με τη δεύτερη, αλλά ακόμη επιδεικνύει σημαντικά πλεονεκτήματα όσον αφορά το κοσμητικό αποτέλεσμα, το μετεγχειρητικό πόνο, και την ικανοποίηση των ασθενών. Επιπρόσθετα, είναι προτιμότερη από άλλες ελάχιστα επεμβατικές τεχνικές, καθώς επιτρέπει βίντεο-υποβοηθούμενη BNE και ταυτόχρονη θεραπεία παθήσεων του θυρεοειδούς αδένα. Το σχετιζόμενο κόστος αποτελεί ένα ζήτημα, αλλά είναι κάτι που συνεχώς βελτιώνεται. Μια επέκταση του υπάρχοντος φάσματος ενδείξεων της MIVAP επιχειρείται, για θεραπεία της παλυαδενικής νόσου, του οικογενούς και δευτεροπαθούς υπερπαραθυρεοειδισμού, με ενθαρρυντικά αποτελέσματα, δίνοντας κίνητρα για μελλοντική έρευνα στο ρόλο αυτής της τεχνικής στη χειρουργική αντιμετώπισης της κοινής αυτής ενδοκρινικής νόσου.

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