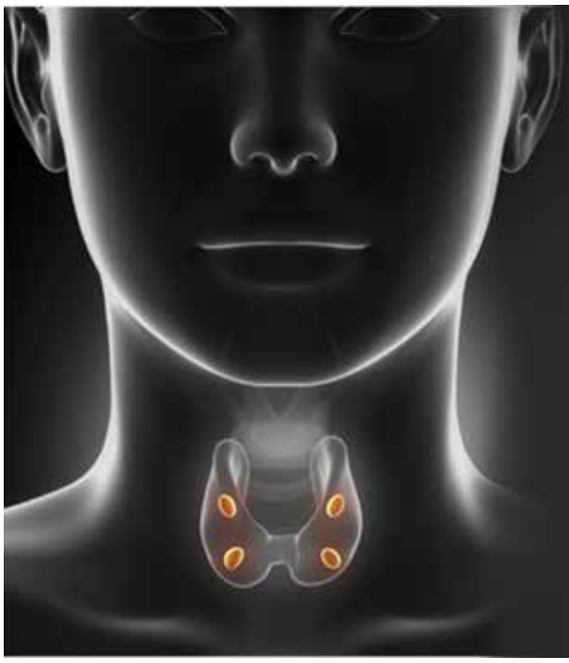

Keyhole Parathyroid Surgery –

a cost-effective treatment of hypercalcaemia

Hypercalcaemia is a common clinical problem, with up to 35 cases per 1000 people in Europe. Calcium plays an important role in intracellular and extracellular metabolism, controlling processes such as nerve conduction, muscle contraction, coagulation and electrolyte regulation. As such the effects of hypercalcaemia are multiple and well summed up in the mnemonic 'Stones, Bones, Groans & Moans'.

Hypercalcaemia causes excess calcium production which exceeds renal capacity for reabsorption. Calcium therefore spills into urine, where it mixes with phosphate and leads to nephrolithiasis (stones). Hypercalcaemia also causes dehydration, leading to a corresponding further increase in serum calcium concentration.

It can also increase gastrin production, leading to increased acidity, so peptic ulcers may occur (groans), and neuropsychiatric symptoms can include depression, irritability, and memory loss (moans). Other prominent symptoms include fatigue and weakness.

Most patients present with mild hypercalcaemia and very few overt symptoms, however hypercalcaemic emergencies do exist. Severe hypercalcaemia (>3.75 mmol/l) is considered a medical emergency, and can lead to coma and cardiac arrest. The effects of elevated calcium on cardiac muscle meanwhile include a shortened QT interval and increased risk of cardiac arrest.

Primary Hyperparathyroidism (PHPT):

Primary hyperparathyroidism (PHPT) is caused by excessive secretion of parathyroid hormone (PTH), which leads to increased bone resorption by osteoclasts (bone cells that reabsorb bone tissue), and increased calcium absorption by the kidneys and intestines.

Table 1

Selected Causes of Hypercalcemia
Excess of parathyroid (PTH) Primary and tertiary hyperparathyroidism Ectopic PTH secretion
Excess of vitamin D: granulomatous (e.g.sarcoidosis)
Excess of calcium intake: "milk-alkali" syndrome
Malignancies (e.g. bone deposits, myeloma)
Drugs Thiazide diuretics Vitamin D and analogues
Miscellaneous Immobilty Familial hypocalciuric hypercalcemia

It is by far the most common cause of raised calcium levels, and together with malignancy, is responsible for more than 90% of all cases. Primary HPT occurs most commonly in patients over 50 and affects three times as many women as men. The incidence ranges from 3 - 20 cases per 1000 adults in different European countries. Other causes of hypercalcaemia may be grouped into those secondary to raised parathyroid hormone (PTH) levels and those mediated by other factors (see Table 1).

In approximately 85% of cases, PHPT is caused by a single adenoma, (in the remaining cases, multiple glands are involved). Primary hyperparathyroidism can also be by caused by parathyroid carcinoma, but this is rare. Familial cases can occur either as part of the multiple endocrine neoplasia syndromes (MEN 1 or MEN 2a), familial isolated hyperparathyroidism (FIHPT) and Familial hypocalciuric hypercalcemia (FHH).

Diagnosis

The diagnosis of PHPT requires an elevated serum calcium level, with simultaneous demonstration of elevated PTH levels (or inappropriately (upper) normal levels in 10% of patients). (see Table 2 over the page)

Measuring urinary calcium excretion over a 24-hour urine collection is important to rule out familial hypercalcemic hypocalciuria. FHH is associated with low calcium excretion (lower than 150 mg/day) and is not surgically treatable.

Table 2

Interpreting Laboratory Values in Hypercalcaemia					
Condition	**Serum Phostphate**	**Serum Alkaline Phosphatase**	**Urine Calcium**	**Urine Phostphate**	**PTH**
Hyperparathyroidism	Low	Normal-high	High (in 67% of patients)	High	High
Vitamin D excess	Normal-high	Low	High	High	Low
Malignancy	Often low	High (except in haematological malignancy, when normal)	Variable	High	Variable
Granulomatous disease	Normal-high	Normal-high	High	Normal	Low
Calcium alkakli syndrome	Normal-high	Normal	Normal	Normal	Low
Familial hypocalciuric hypercalcaemia	Normal or low	Normal	Low (<200mg/day)	Normal	High

A careful family history is key in recognising familial forms of primary HPT. In these cases, urinary screening for catecholamine overproduction is important before surgical treatment to exclude a phaeochromocytoma (tumour of the medulla of the adrenal glands).

Treatment – Parathyroid Surgery

Parathyroid surgery remains the only curative and most cost-effective treatment option in PHPT, and requires removal of all abnormal parathyroid tissue. Long-term cure of HPT is achieved in over 95% of patients, along with significant improvement in associated symptoms.

All patients with significant and/or symptomatic PHPT should be referred for surgical treatment. In symptomatic patients, studies have shown that bone density improves and fracture rate declines after parathyroidectomy, and cognitive function also appears to improve. In patients who had kidney stones before surgery, the incidence declines after surgery. Cardiovascular disease and premature death also appear to decrease after surgery in symptomatic subjects.

Historically, there has been more uncertainty on the role of surgery in milder and apparently 'asymptomatic' cases. However many so-called 'asymptomatic' patients report neurocognitive symptoms when specifically questioned. New data on the natural history of 'asymptomatic' PHPT have also favored surgery because bone density does not appear to be indefinitely stable.

Moreover, up to a third of patients who are monitored long-term develop signs of disease progression, so surgery may eventually be appropriate in the majority of patients with asymptomatic disease. The argument is stronger for younger patients (<50 years) and for those whose bone density is low or falling.

There is increasing data to show the benefits and symptom improvements after surgery in 'asymptomatic' patients:

- Improvements in Neuropsychiatric symptoms and quality of life
- Improved Bone density and reduced fracture risk
- Reduced risk for premature death & excessive mortality (cardiovascular disease).

Finally, because no effective medical therapy for HPT exists, all patients with HPT who are otherwise healthy should be considered for surgical treatment.

Traditional 'open' bilateral neck exploration:

Since the first parathyroidectomy in 1925, a bilateral exploration of the neck has traditionally been performed to identify all (typically four) parathyroid glands, assess which are abnormal and remove only these. This is an invasive technique requiring a 5-7cm incision in the neck, with patients remaining in hospital for 1-3 days. It remains the most common technique for many surgical units, particularly for the less common 4-gland hyperplastic disease.

Minimally-invasive keyhole Parathyroid surgery:

With the advent of automated blood analysers in 1970s, most patients are now incidentally identified and present with 'asymptomatic' mild hypercalcaemia. For these patients the above-mentioned open surgery became unsatisfactory, and a less invasive alternative was required.

Over the last 20 years there have been major advances in surgical technology, allowing for easier and quicker keyhole surgery with reduced morbidity & complications (Fig 1). More advanced diagnostic imaging also enables pre-operative localisation of the abnormal parathyroid gland(s) and makes a more targeted surgical approach possible (Fig 2).

An evolution of parathyroid surgery has occurred as a result, towards a more targeted, minimally-invasive technique with the opportunity for daycase surgery.

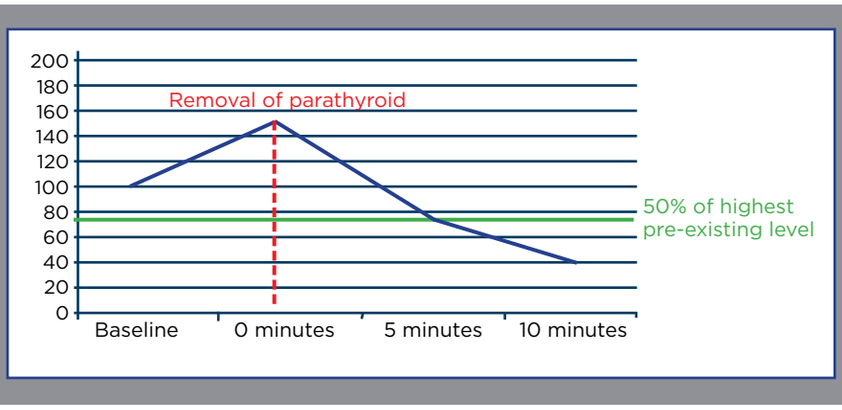

Fig. 1 The Intra-operative rapid-PTH assay, capitalises on the very short natural half-life of PTH (< 5mins) and allows biochemical confirmation of cure only 10 mins after removal of the abnormal adenoma. This enables the surgeon to exclude the possibility of mutli-gland disease and ensures all abnormal glands have been removed.

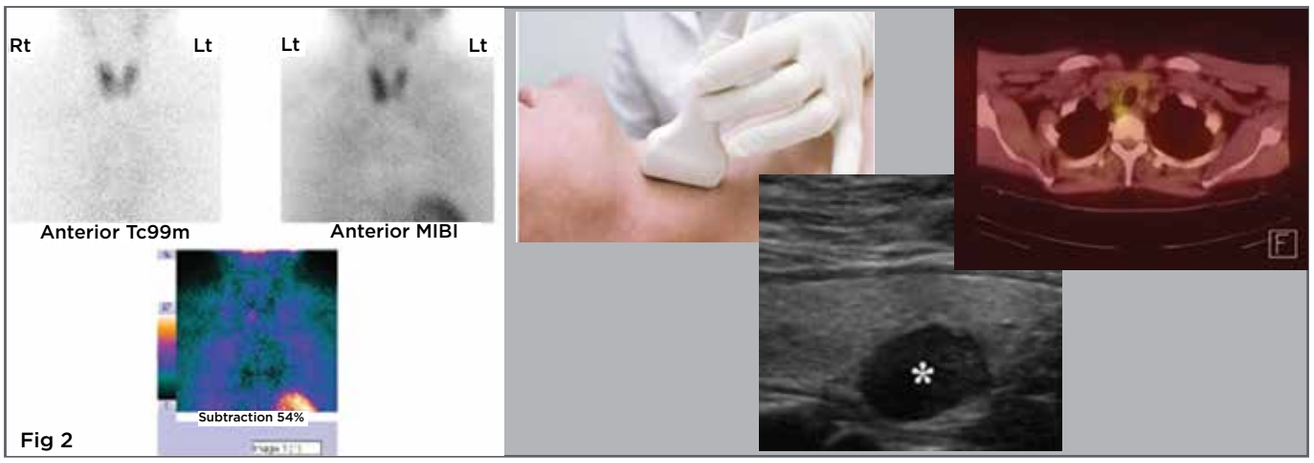

Fig 2

Minimally-invasive keyhole parathyroid surgery has become more popular with patients and primary care physicians alike due to its many benefits:-

- Highly effective: 95+% cure rate
- Shorter Operation
- Less post-op pain & swelling
- Shorter hospital stays/daycase
- Can be done under local anaesthetic & sedation
- Faster recovery
- Improved cosmesis & patient satisfaction
- Cost-effective

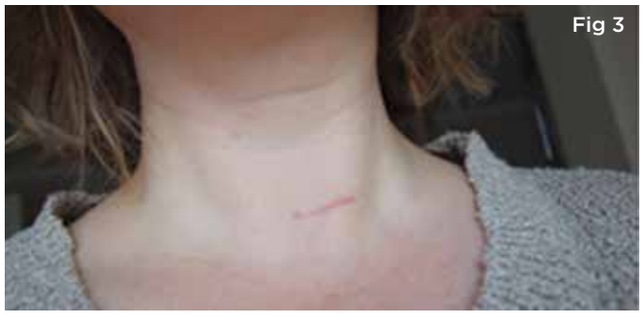
Fig 3

Uni-lateral mini-incision keyhole approach: (Fig 3)

In the earlier stages of the surgical evolution, a mini-incision was placed to one side of the neck directly over the pre-localised abnormal parathyroid gland. This technique had several drawbacks, allowing only one side of the neck to be explored surgically and thus only being applicable to patients with positive findings that agree in 2 different imaging modalities.

This occurs in 50-60% of patients. So over 40% are deemed unsuitable for the keyhole technique and offered open invasive surgery, as keyhole surgery may need to be converted to open surgery if the adenoma is not easily identified on the presumed side. Also it is not possible to explore the contra-lateral neck in cases of multi-gland disease, resulting in reported higher recurrence rates. The resultant scar is off-centre, asymmetric and more conspicuous.

Bi-lateral mini-incision keyhole approach: (Fig 4)

More recently, a central approach using a 2cm mini-incision overcomes many of the limitations of the unilateral approach by allowing full exploration of the neck on both sides. The Norman group in the USA has demonstrated excellent cure rates (>97%) amongst 15,000 patients with minimal disease recurrence, and after changing our practice from a unilateral to bilateral keyhole technique we have shown similarly excellent cure rates in over 100 patients (>97%).

As the technique allows bilateral neck exploration, it is less dependent on pre-surgery localisation of the abnormal glands, so is suitable for the majority of patients. We have shown a very low conversion-to-open rate (less than 10%), and as the scar is central and symmetrical the final cosmetic outcome is far superior.

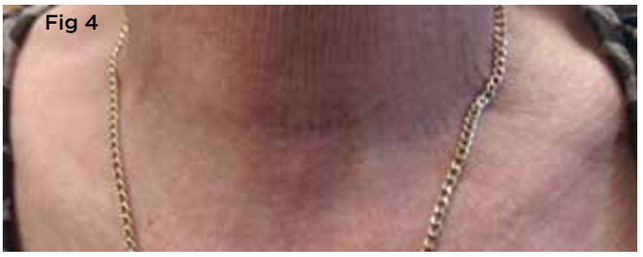
Fig 4

Medical Treatment and Surveillance

Patients not treated surgically should be managed to ensure good hydration and avoid thiazide diuretics. In patients with symptomatic and significant hypercalcaemia, bisphosphonates may be used to lower the serum calcium level, although they are usually not symptomatically effective. Treatment with Cinacalcet (a calcimimetic drug which activates the calcium-sensing receptor and inhibits parathyroid cell function) results in calcium reduction without normalisation of parathyroid hormone levels. However, it has not shown to increase BMD and evidence of other health benefits is lacking.

Asymptomatic patients who choose not to have surgery should be carefully monitored for overt signs and symptoms of primary hyperparathyroidism on an annual basis, including annual serum calcium and creatinine levels. A 3-site dual-energy radiographic absorptiometry study should also be obtained every 1-2 years (2009 NIH Guidelines).

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