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Education and Training Update

Parathyroid Surgery for Primary Hyperparathyroidism in 2026

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Abstract

Primary hyperparathyroidism (PHPT) is the most common parathyroid disease and one of the most common endocrine disorders. It results from autonomous overproduction of parathyroid hormone, which in the classic form of the disease causes hypercalcaemia. The ready access to biochemical testing in high-income countries has moved the disease spectrum from a classic symptomatic presentation to a biochemical anomaly that is asymptomatic or minimally symptomatic. Untreated PHPT, however, remains associated with significant consequences. This review summarizes up-to-date concepts in the diagnosis, imaging, and surgical management of PHPT. The diagnosis of PHPT requires confirmation of hypercalcaemia with inappropriately elevated or unsuppressed parathyroid hormone levels, while excluding alternative causes. Parathyroidectomy remains the only definitive cure for PHPT, and the changing thresholds for intervention are discussed. Advances in pre-operative localization, including high-resolution ultrasonography, 99mTc-sestamibi (technetium-99m methoxyisobutylisonitrile), 4D-computed tomography, and fluorocholine positron emission tomography, have increased the number of patients with localised disease and therefore facilitated focused and minimally invasive surgical approaches. Intraoperative parathyroid hormone monitoring has also added a new dimension to intraoperative decision-making. However, the single biggest determinant of outcome in parathyroidectomy remains the practice volume and experience of the operating surgeon. It remains to be seen whether emerging technologies, including robotic surgery, thermal ablation, advanced molecular imaging, and artificial intelligence–assisted diagnosis and lesion localization, will further refine patient selection and improve treatment strategies in PHPT.

Keywords: primary hyperparathyroidism; hypercalcaemia; parathyroid hormone; diagnostic imaging; parathyroidectomy

1. Introduction

Primary hyperparathyroidism (PHPT) is a metabolic disorder characterized by an overproduction of parathyroid hormone (PTH) that leads to elevated levels of serum calcium [1]. It is the commonest disease of the parathyroid glands and is now the 3rd commonest endocrine disorder worldwide, affecting 0.1% of the general population [2,3]. It can occur in all age groups with a peak incidence/detection in the 6th decade. Under the age of 40 years, the sexes are equally represented, but female dominance increases with age such that prevalence among postmenopausal women may be over 1% [4]. PHPT is caused by a set point error for PTH release that is not normally suppressed by a rising calcaemia. The major pathophysiological event in PHPT is an overgrowth of clonally dysregulated parathyroid tissue with excessive secretion of parathyroid hormone and decreased expression of cell surface calcium-sensing receptor (CaSR) [5]. This culminates in the need for higher levels of calcaemia to suppress PTH release—a shift to the right of the calcium versus PTH curve [6]. Under normal physiological conditions, PTH is essential to maintain normocalcaemia and influences bone remodelling, impacting both bone formation and resorption. Increased and continuous PTH-mediated stimulation results in hypercalcaemia, resulting from increased bone turnover with an excess of bone resorption over formation [7]. PTH also increases reabsorption of calcium from the distal renal tubules in the kidney and increases excretion of phosphate from the proximal tubules. It also causes increased intestinal absorption of calcium and phosphate [8].

The diagnosis of PHPT in its classic form requires hypercalcaemia coupled with elevated or unsuppressed PTH levels in the presence of an optimized serum vitamin D and normal kidney function [3]. The table below lists the common differences between PHPT and the other common cause of hypercalcaemia - malignancy-associated hypercalcaemia (Table 1, Ref. [9]).

In patients with hypercalcaemia and a non-suppressed PTH, it is essential to exclude benign familial hypocalciuric hypercalcaemia (FHH), a genetic abnormality that can be present in up to 2% of patients with this biochemistry. Estimating the calcium-to-creatinine urinary clearance ratio can help exclude this condition. FHH is likely when the ratio is <0.01 and is least likely when >0.02. However, most patients reside in the grey zone between these key 2 values, so when in doubt, genetic testing with a parathyroid genetic testing panel should be considered (see below) [10].

In recent years, in addition to classic type PHPT, other variants of the disease have been described, such as *normohormonal PHPT*—inappropriately normal PTH in a patient with hypercalcaemia [11]—and a *normocalcaemic PHPT* where the serum calcium is normal but with an inappropriately raised PTH. To make this diagnosis reliable, other

Table 1. Differences in biochemical parameters between PHPT and malignancy-associated hypercalcaemia [9].

Test (plasma)	Malignancy-associated hypercalcaemia	PHPT
Calcium	Very high	High
Phosphorous	Low[a]	Low or normal
PTH	Suppressed	Inappropriately elevated or unsuppressed
Urinary Calcium	High	Normal/High

[a] Exceptions include osteolytic metastasis and lymphoma-associated hypercalcaemia. PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

causes of the biochemistry must be excluded, and the tests should be repeated over 6 months to avoid over-diagnosis [1,12]. Normocalcaemic PHPT (NHPT) remains a controversial entity, but when the diagnosis is robust, up to a third of cases may progress to the classic variant and/or symptomatic disease [3]. NHPT often has comparable symptomatology to classic hyperparathyroidism, and the benefits of parathyroidectomy overlap with those of classic PHPT. NHPT is, however, associated with a higher incidence of double adenomas and hyperplasia, and lower cure rates. It is hence preferable that these cases be referred to high-volume endocrine surgery centers, as they are more used to managing such complex cases [13].

PHPT is often underdiagnosed, and the most common cited reason is cognitive overload. Electronic medical record (EMR) and machine learning-based solutions have been studied as a tangible solution to help with earlier and more accurate diagnosis [14]. Machine learning models have been developed to help clinicians identify both straightforward and atypical PHPT cases, and some of these models have demonstrated high specificity and negative predictive values in the diagnosis of PHPT (92.9% and 99.1%, respectively, in atypical PHPT) [15].

2. Aetiology of PHPT

PHPT is sporadic in over 90% of cases and is most frequently caused by a benign growth within one or more parathyroid glands [16]. In addition to a family history, known risk factors for PHPT include ionizing radiation exposure and chronic lithium use [11]. Familial hyperparathyroidism encompasses several hereditary syndromes, including multiple endocrine neoplasia type 1 (MEN1), familial isolated primary hyperparathyroidism (FIHP), multiple endocrine neoplasia type 2 (MEN2), and hyperparathyroidism–jaw tumour (HPT-JT) syndrome. Among these, MEN1 is the most frequent, followed by HPT-JT, MEN2, and FIHP. 10–30% of patients with a clinical diagnosis of MEN1 have no identifiable pathogenic MEN1 mutation, which may reflect mutations in non-coding or regulatory regions or large genomic rearrangements. Furthermore, carriers of the same pathogenic variant, including members of the same family and monozygotic twins, may exhibit considerable phenotypic variability [17]. Additional genes commonly included in multigene testing panels for hereditary PHPT include *CDC73*, *GCM2*, *CDKN1A*, *CDKN1B*, *CDKN2B*, *CDKN2C* and *RET*. For hereditary syndromes caused by mutations in tumour suppressor genes, such as *MEN1*, *CDC73*, *CDKN1A*, *CDKN1B*, *CDKN2B*, and *CDKN2C*, inheritance of a germline pathogenic variant in one allele typically represents the first "hit" in Knudson's two-hit model of tumorigenesis. Subsequent somatic inactivation of the remaining wild-type allele results in complete loss of tumour suppressor function and promotes tumour development. In contrast, RET-associated MEN2 results from activating mutations in a proto-oncogene and does not follow the classical two-hit mechanism [17]. The availability of genetic testing allows the identification of syndromic disease in a majority of these cases and is indicated in patients with a family history or in patients who have had the disease under the age of 30 years [18]. Genetic testing should also be considered in patients under 40 years old when other factors such as a family history, recurrent disease, or multiple gland disease are present. Genetic testing has a crucial role in the diagnosis and treatment of familial hyperparathyroidism and shapes the optimal surgical strategy, allows the follow-up of non-parathyroidal lesions, guides family screening, quantifies the risk of developing parathyroid cancer, and helps avoid inappropriate surgery in FHH [19].

3. Clinical Features

Traditionally, PHPT presented with Fuller Albright's aphorism of *bones, stones, abdominal moans, and psychic groans* [20]. However, the arrival of the multichannel serum autoanalyzer in the 1970s led to an earlier diagnosis of the disease due to the unveiling of a reservoir of subclinical disease [21]. As a consequence, PHPT now usually presents in high-income countries as what is loosely called asymptomatic disease. Indeed, severe and symptomatic disease, characterized by 'stones, bones and groans', is the more common manifestation in lower-income countries where access to healthcare results in a delayed diagnosis [11,22]. Data from the Indian PHPT registry indicate that over 90% of the diagnosed disease is symptomatic, although in the decade from 2010, there is an increasing trend of less symptomatic disease [23]. This relates to an earlier diagnosis and is attributable to improved health-care access and awareness [24]. A similar pattern is emerging in China as affluence increases [25]. The significant difference in the reported incidence of PHPT between the Western world

and the Asian population may also be related to nutritional, genetic, and environmental factors [26]. The developing world is also seeing a rising trend in the diagnosis of secondary or tertiary hyperparathyroidism (HPT), and this is attributed to improved awareness among physicians and increased lifespan in chronic kidney disease because of better availability and accessibility of renal replacement therapy [27].

Patients with PHPT have 40 times the background population's risk of renal calculi, and indeed urinary tract stones are currently the most common presenting symptom in symptomatic PHPT patients [28]. Between 2 and 8% of patients with renal calculi have PHPT, and the prevalence increases if scanning for end-organ damage is routinely performed in newly diagnosed PHPT patients [29]. Other features of end-organ damage include bone loss detected on bone mineral density, and less commonly pathological fractures or osteitis fibrosa cystica. Subtle neurocognitive, musculoskeletal, and gastrointestinal symptoms are also not uncommon but do not usually correlate with calcium levels [3]. Calcium pyrophosphate crystal deposition is occasionally seen in PHPT and can cause calcification in the joint capsule and fibrocartilage. Pseudogout in such patients may present when calcium levels normalize after parathyroid surgery [12].

4. Indications for Parathyroid Surgery

Surgery is currently the only definitive treatment for PHPT [22]. Observation and medical management are less cost-effective and less efficacious than surgery in preventing the long-term deleterious effects of PHPT in both symptomatic and asymptomatic cases [30]. Whilst there is universal agreement on the need for parathyroid surgery in patients with end-organ damage, consensus statements were required to agree on the threshold for parathyroid surgery in asymptomatic disease.

Over the past 30 years, the surgical indications for asymptomatic primary hyperparathyroidism (PHPT) have gradually expanded. In 1990, the National Institutes of Health (NIH) consensus conference recommended that surgical treatment should be considered for asymptomatic patients with serum calcium levels 1–1.6 mg/dL (0.25–0.4 mmol/L) above the upper limit of normal, a dual-energy X-ray absorptiometry (DXA) Z-score $\leq$–2.0 at any site, or an age less than 50 years. Subsequent guidelines have gradually lowered the intervention threshold. By 2008, the serum calcium standard had been refined to >1 mg/dL (0.25 mmol/L) above the normal value, the bone mineral density standard had been changed to a T-score $\leq$–2.5 at any site, and the renal function standard had added eGFR <60 mL/min. In 2013, the skeletal criteria were further refined to include the lumbar vertebrae, femoral neck, or distal radius, and vertebral fractures detected by imaging were also included as an indication; the scope of kidney assessment was expanded to include biochemical stone risk analysis and evidence of nephrocalcinosis or kidney stones [5].

The more recent 5th international consensus workshop detailed below has gravitated towards thresholds for surgery in symptomatic and asymptomatic disease [5].

• All symptomatic patients

• Asymptomatic patients:

- <50 years;

- Glomerular filtration rate (GFR) or creatinine clearance is <60 mL/min;

- Evidence of renal calcifications, nephrocalcinosis, or urinary stones;

- Hypercalciuria (>300 mg/24 hours men / >250 mg/24 hours women);

- Osteoporosis (T-score $\leq$–2.5 at distal radius, lumbar spine, total hip or femoral neck) or vertebral compression fractures by X-ray, computed tomography (CT), magnetic resonance imaging (MRI) or vertebral fracture assessment;

- Serum calcium >1 mg/dL (0.25 mmol/L) >upper limit of normal.

The UK National Institute for Health and Care Excellence (NICE) guidelines have followed a similar path but have added a health economic perspective, and consequently, it is recommended that surgery be considered because there is no medical management that is as cost-effective as parathyroid surgery. The UK NICE guidelines recommend referral to a parathyroid surgeon for all patients with a confirmed diagnosis of PHPT and symptoms of hypercalcaemia, such as thirst, frequent or excessive urination or constipation, or evidence of renal stones, osteoporosis or fragility fractures, and those with adjusted calcium >2.85 mmol/L [31]. Those patients who do not meet this threshold should be considered for surgery too, so that nearly all patients are potential surgical candidates. Indeed, conservative management of PHPT is indicated only in cases where the patients are high risk for surgery or anesthesia because of significant co-morbidities [22,30]. A recent authoritative evidence-based review comes to a similar recommendation [32].

5. Parathyroid Imaging

In 1931, Edward Churchill, head of surgery from Massachusetts General Hospital, stated that "*the success of parathyroid surgery must rely on the ability of the surgeon to know a parathyroid gland when he sees it, to know the distribution of the glands, where they hide, and also be delicate enough in technique to be able to use this knowledge*" [33]. Almost 100 years have passed, but the principles of parathyroid surgery remain the same. However, parathyroid surgery has been facilitated by the arrival of pre-operative imaging as well as some technological adjuncts.

Whilst pre-operative localization studies have no role in the diagnosis of PHPT, they may aid identification of the abnormal gland and therefore facilitate targeted surgery

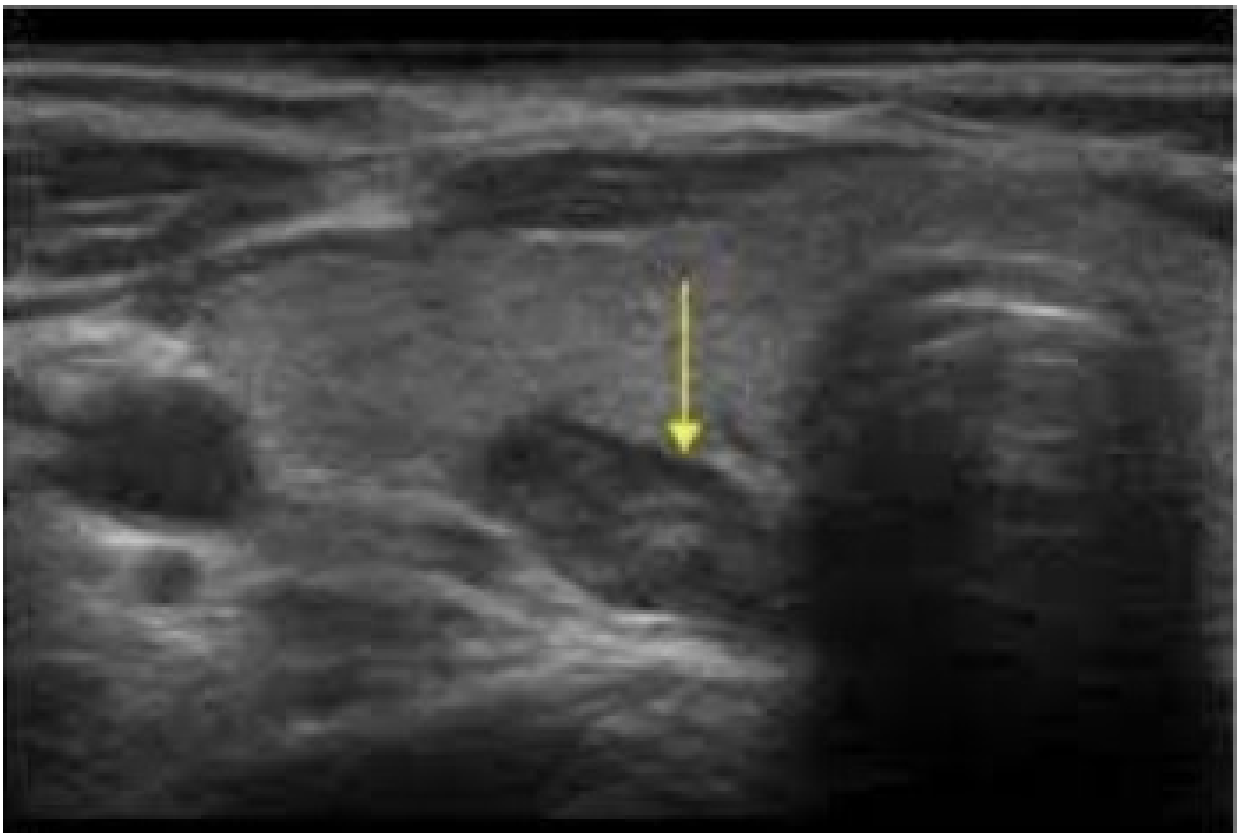

Fig. 1. High resolution ultrasound showing the typical appearance of a parathyroid adenoma. The yellow arrow indicates an ovoid parathyroid lesion posterior to the thyroid gland.

[30]. The only indication for parathyroid imaging is surgical planning, and it should not be used as a tool for diagnosis or risk stratification [34]. Targeted or *minimally invasive* parathyroid surgery aims to remove the single offending parathyroid without the need to seek or identify the other glands. This is further optimized by using intraoperative PTH measurements, first popularized by Irvin and colleagues [35]. Pre-operative localization helps in appropriate surgical planning and can enable minimally invasive parathyroidectomy, which is associated with shorter operative time, lower complication rates, and reduced hospital stay [36].

A range of localization studies are currently in use, and the modality varies geographically, largely governed by resources, access, and expertise. High resolution neck ultrasound (USS) is the most widely used first-line imaging modality due to the ease of accessibility, low cost, absence of radiation, and the ability to exclude concomitant neck pathology [16,30]. Parathyroid adenomas appear as well-defined, hypoechoic nodules, separate from the thyroid gland and separated by a thin echogenic capsule on grey scale ultrasound (Fig. 1) [37]. The limitations of ultrasound are that it is operator dependent, of limited use in the presence of multi-nodular goitre, and less effective in localization of deep-seated parathyroids such as retro-tracheal and retro-esophageal glands [16].

The most widely used functional imaging is 99mTc-sestamibi (technetium-99m methoxyisobutylisonitrile) (Fig. 2) or double tracer using 99mTc-pertechnetate and 99mTc-sestamibi subtraction imaging [16]. 99mTc-sestamibi scanning is based on the preferential uptake and retention of radiotracer-methoxyisobutylisonitrile (MIBI) in the mitochondria-rich cells of the parathyroid glands. Combined with single-photon emission computed tomography (SPECT), it provides combined functional and anatomical images in PHPT. However, it offers low spatial resolution [38].

An alternative to 99mTc-sestamibi scanning is 4D-computed tomography (4D-CT) scanning. As is often the case with imaging, this was originally introduced in a re-operative setting, but is now increasingly used as a first-line alternative to 99mTc-sestamibi scanning when the radiological expertise is available [38]. This imaging is based on the principle that parathyroids have low attenuation on an unenhanced image but enhance and wash out rapidly during the arterial, venous, and delayed venous phases (Fig. 3). In contrast, lymph nodes show progressive enhancement and thyroid tissue, which is hyperdense on unenhanced images, retains the contrast for longer [34].

Axial T1 and T2 weighted magnetic resonance imaging pre- and post-contrast, along with fat suppression sequences, has also been used for parathyroid adenoma lo-

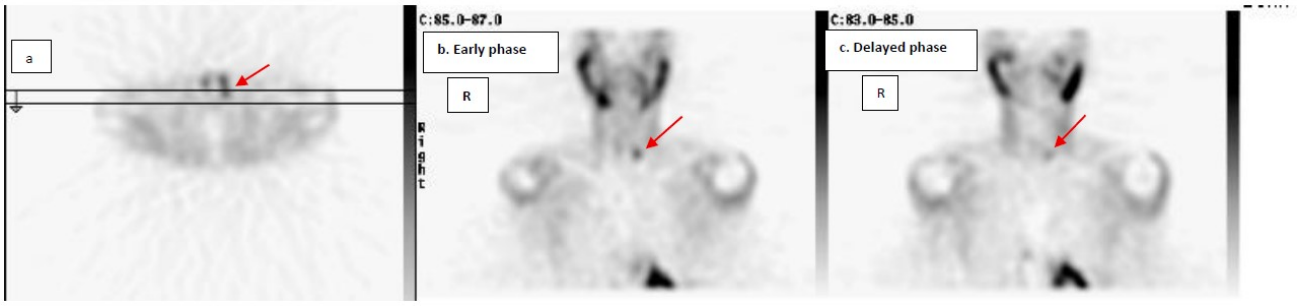

Fig. 2. 99mTc-sestamibi scan. This demonstrates focal uptake in the region of the lower pole of the left lobe of the thyroid seen on planar images (a) and in the early phase imaging (b) and retained uptake in the delayed phase (c), raising suspicion for a left inferior parathyroid adenoma (marked with red arrow). 99mTc-sestamibi, technetium-99m methoxyisobutylisonitrile.

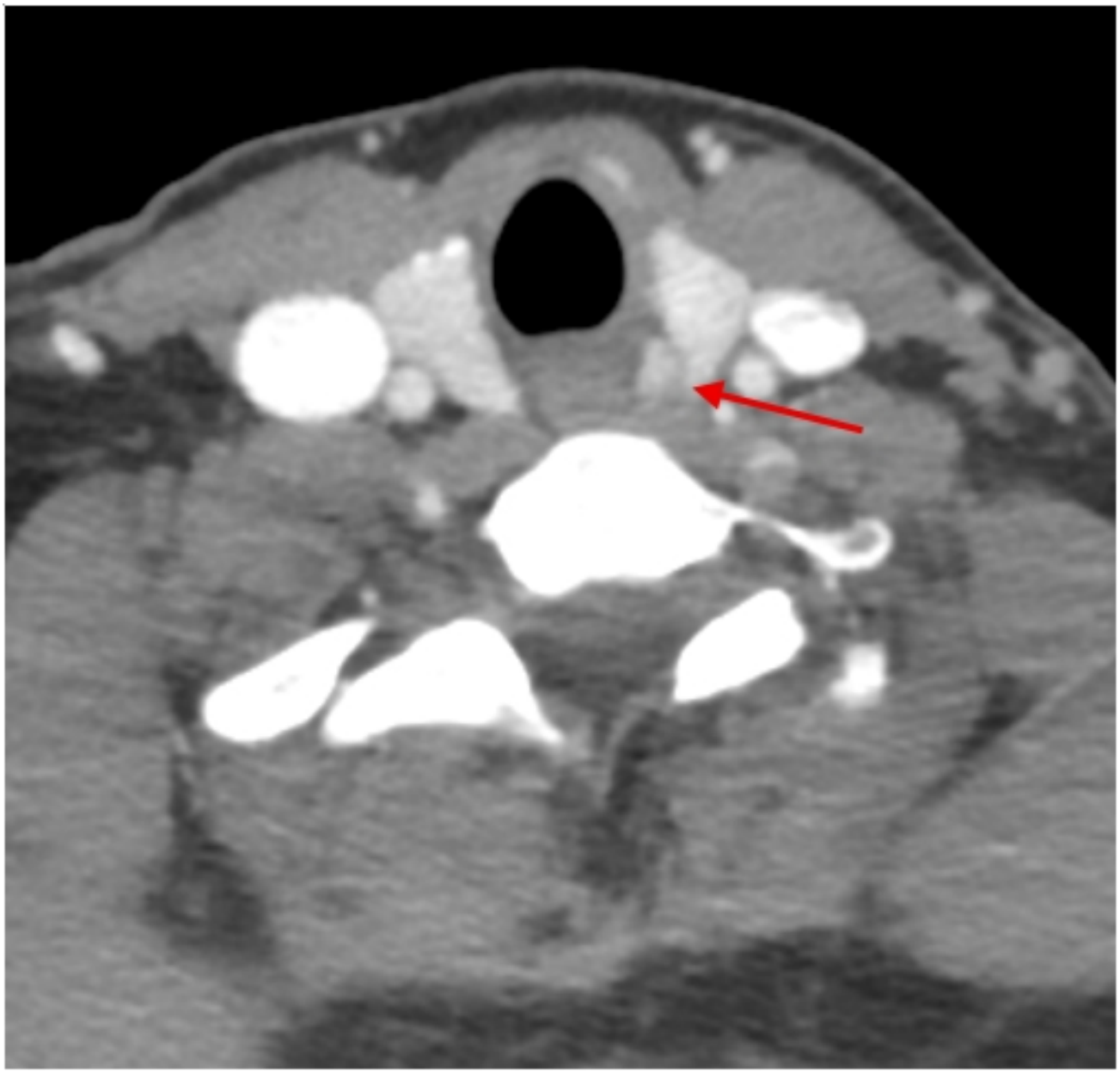

Fig. 3. 4D-CT at 30 sec post contrast showing a left superior parathyroid adenoma marked by a red arrow. 4D-CT, 4D-computed tomography.

calization; however, the sensitivity varies from 43.4% on a 1.5T MRI to 97.8% on a 3T MRI. Its sensitivity decreases in the presence of multi-gland disease, and the appearance of parathyroid adenoma closely resembles ectopic thyroid tissue or lymph nodes [39]. 4D-magnetic resonance imaging (4D-MRI) protocols similar to 4D-CT makes use of the hypervascular nature of parathyroid adenomas for detecting the lesion, and the combined use of USS, SPECT and 4D MRI can help increase the rate of localization. MRI can be considered in younger patients as an alternative imaging modality to reduce radiation exposure [40].

A more recently introduced modality that has shown great promise is ^{18}F-fluorocholine positron emission tomography/computed tomography (^{18}F-CH positron emission tomography computed tomography) (Fig. 4) with a reported sensitivity of 99% in cases with negative or discordant first-line imaging. Routine use is currently limited in most countries because of availability and high cost involved [39]. It is currently mainly used as a second-line imaging modality in re-operative surgery and has produced excellent results, especially in ectopic parathyroid glands [34]. The APACH2 trial demonstrated first-line use of ^{18}F-CH PET CT (FCH1) to be highly effective and a safe replacement to first-line use of MIBI (MIBI1), however was more expensive. It is suggested that it improves patient comfort, reduces radiation exposure, and the need for second-line investigations by leading more patients directly to less exploratory surgery and normalization of calcium as compared to MIBI at a small additional cost. From a cost-benefit ratio and health insurance perspective, use of FCH1 in the pre-operative localization in PHPT can help more patients to be directed to out-patient parathyroidectomy as compared to MIBI1 [41] but this is a debatable conclusion when in some institutions all surgery has been performed on a day-case basis for many years.

The difference in rate of positivity between choline PET CT and MIBI may be explained by the cellular makeup of the parathyroid adenomas. Choline uptake is higher in chief cells, and these chief cells are also known to have higher metabolic turnover than oxyphil cells, which may explain the higher ^{18}F-CH PET CT uptake in this specific subset. There have also been reported associations of choline avidity and elevated PTH levels, supporting its ability to showcase the physiological activity of hyperactive parathyroid tissue [42].

Other localisation modalities, like venous sampling and fine needle aspiration (FNA) of parathyroid adenomas, are reserved for re-operative surgery [30,43]. Selective venous sampling involves collecting PTH samples from different zones of the neck veins to establish a gradient and localize the probable site of the adenoma [3].

It is uncontroversial to say that ultrasound is the first-line imaging of choice, to which a single ionizing radiation modality can be used to complement it. Whether this is MIBI, 4D CT or choline PET is a surgical preference coupled with local protocols that have provided the best outcomes [37].

Deep learning (DL) based localization using ^{18}F-CH PET CT has been suggested as a promising modality for pre-operative localization in PHPT—with an accuracy of 83% and 74% accuracy in identifying the quadrant of hyperfunctioning parathyroid tissue. The DL methods performed worse statistically ($p < 0.001$) in both tasks compared to human readers, who localise PHPT with an accuracy of 97.7% [44]. The use of machine learning tools remains experimental, and most studies to date have used few patients to train these models and/or use multiple frames and videos from one patient. The risk of bias in machine learning due to sharing of data from the same origin is inherent, but this technology may find a role in the future [45].

6. Parathyroid Surgery in 2026

PHPT is caused by a single adenoma in over 85% of patients [22]. Other combinations of multiple-gland involvement accounting for the remaining 15% include multiple adenomas or hyperplasia [30]. Parathyroid cancer is encountered in under 1% of cases [2,22]. Focused or minimally invasive parathyroid surgery should in theory be possible in up to 85% of cases if the localization studies were reliably able to identify single gland disease in all cases. This, however, is not the case. Parathyroid disease that is unlocalized can be cured in the vast majority of cases in specialist centers, so failure to localize the disease pre-operatively should not represent a contraindication to surgery when the clinical threshold for intervention is reached [46].

Parathyroid surgery can be performed as a day-case or 23-hour stay surgery, especially in localized disease in nearly all patients. Ideal candidates for day care parathyroidectomy include those with well-localized parathyroid lesions, limited co-morbidities, stable socio-economic status, and reliable access to post-operative support [47]. The surgery is usually performed under general anesthesia; however, it can also be performed under local anesthesia if the lesion is confidently localized [48]. Perioperative antithrombotic therapy is usually not indicated in parathyroidectomy and its use should be individualized based on the drug's half-life, renal function, and the patient's thromboembolic and bleeding risk assessment. Appropriate interruption of anticoagulant and antiplatelet therapy is essential to minimise the risk of post-operative cervical hematoma while avoiding unnecessary thrombotic complications. Prophylactic antibiotics and post-op anticoagulation are not routinely indicated unless other co-morbidities necessitate their use. Sequential compression devices should be applied to reduce the risk of deep vein thrombosis [8].

The definition of cure after parathyroidectomy is the normalization of serum calcium levels for at least 6 months after surgery. In normocalcaemic PHPT, cure is defined

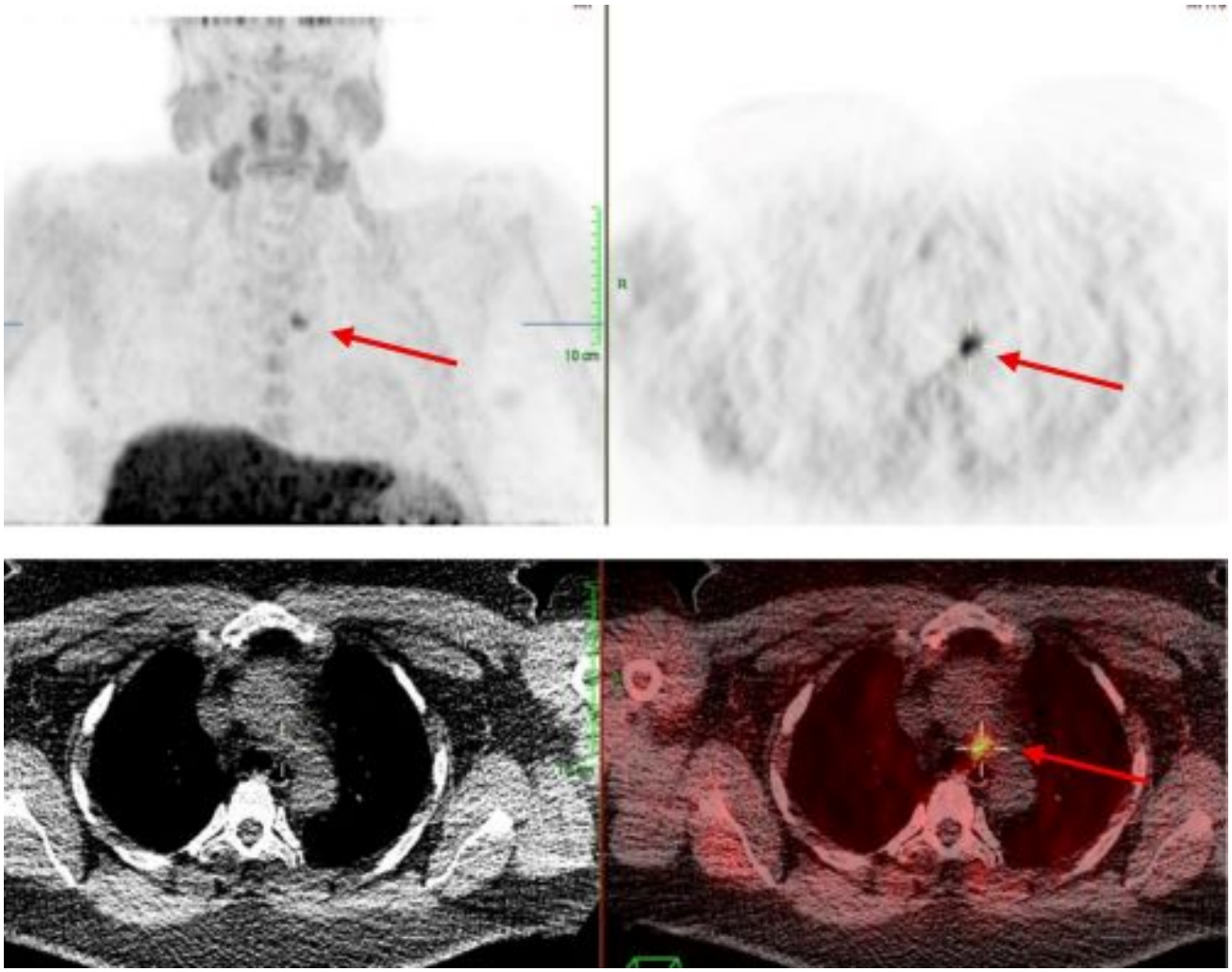

Fig. 4. ^{18}F-fluorocholine PET CT showing a solitary focus of increased activity in the mediastinum suggestive of ectopic parathyroid adenoma, which is marked with three red arrows. PET, positron emission tomography; CT, computed tomography.

as the complete normalization of biochemistry, including PTH, for more than 6 months after surgery. Failure to achieve a cure in the 6 months' time frame is *persistent PHPT*. If the disease recurs after this time, then it is described as *recurrent PHPT*. The diagnosis of recurrence requires completely normal biochemistry for at least 6 months after surgery [30]. True recurrent PHPT is uncommon, and the most common reason for persistent hyperparathyroidism after surgery is the failure to identify the abnormal gland at the first surgery or the failure to detect multiple gland disease [49]. A proportion of patients cured after a parathyroidectomy will have post-parathyroidectomy normocalcaemic PTH elevation [50]. This phenomenon is incompletely understood and is seen most often in older patients, those with higher pre-operative PTH, low vitamin D status, and impaired renal function. In some, however, it may be a harbinger of recurrent PHPT, especially in targeted surgery [51].

Many technology-driven surgical approaches to targeted parathyroid surgery have been used, including endoscopic parathyroidectomy [52], minimally invasive video-assisted parathyroidectomy (MIVAP) [53], remote access approaches such as robotic approaches [54] and more recently trans-oral approaches [55]. Endoscopic procedures have their inherent limitations such as two-dimensional view, need for CO_2 insufflation, fulcrum effect and limited instrument mobility, especially in confined spaces [56]. Robotic surgery promises better visualization, improved dexterity, and finer instrument control, all of which are essential for a precise and delicate operation like parathyroidectomy, however, widespread adoption of robotic parathyroidectomy is limited by its availability, high cost, and the learning curve. Robotic parathyroidectomy may be especially beneficial when operating in narrow and remote anatomical locations such as the mediastinum [57]. Single institution case series of trans-oral robotic parathyroidectomy (TORP) has shown promising results, with the advantage of being able to avoid a neck scar [58], however, the excellent cosmesis achieved by the focused lateral approach and targeted unilateral neck exploration, in general, is such

that most have not gained universal traction. Whichever focused approach is used, it should have the advantage of shorter operative time, less dissection, a low incidence of post-operative hypocalcaemia, and better cosmesis. Other claims such as less pain, shorter hospital stay, and lower hospital cost are questionable and have rarely proved consistently reproducible after the initial period of enthusiasm has passed [59]. Robotic approach via trans-axillary route has also been studied, but this has the disadvantage of muscle stiffness in the pectoral muscles due to extensive dissection away from the gland and also numbness affecting the area around the incision site [57]. Robotic surgeries have been reported to have longer operative times; however, this has not been shown to impact post-operative outcomes including duration of hospital stay and cure rates [56].

Other techniques and devices have also been reported to add value to parathyroid surgery, but it remains difficult to distinguish the well-established benefit of surgical volume and experience [60] from the surgical adjuncts described. A good example is radio-guided parathyroidectomy using a low dose of 99mTc-sestamibi and a hand-held gamma probe [61]. It also remains to be seen whether ultrasound-guided thermal ablative parathyroidectomy can be used in focused disease in the future. It may also be limited to inferior parathyroid adenomas that are likely to be further from the recurrent laryngeal nerve that can be affected by the heat. It can be considered as an alternative to surgery in patients who are high risk for surgery or there are contraindications for surgery. Thermal ablation (radiofrequency ablation or microwave ablation) requires localized disease, ideally in the inferior position, and patients with parathyroid adenomas that cannot be seen on USS should not be managed with thermal ablation. If there is any suspicion of parathyroid malignancy based on imaging or biochemistry, en-bloc surgical excision is preferred unless thermal ablation is considered for palliation [62]. Thermal ablation has been reported to have a lower complication rate, including hypocalcaemia and hoarseness; however, larger randomized studies are required to confirm these reported benefits [63]. It is reported to have a technical success rate of 98% and a cure rate of >95% for nodules >6 mm [64] but long term follow up and post-operative laryngoscopy in larger comparative studies are required.

Targeted surgery has demonstrated that with a small incision, bilateral neck exploration (BNE) can also be performed on patients with unlocalized or discordantly localized disease with high cure rates [46]. The principle of this type of parathyroidectomy is that all the parathyroids should be identified and the pathological glands only removed. Care must be taken to avoid devascularization or removal of normal glands to prevent permanent hypoparathyroidism [8]. Whatever approach to parathyroid surgery is adopted, and in particular, in focused parathyroidectomy, intra-operative PTH (IOPTH) assay allows biochemical confirmation of cure, which may shorten the operating time and possibly improve the cure rate. Rapid IOPTH assay was first developed and introduced into clinical practice by Irvin and colleagues in 1991, and the current assay will give a result in about 5 minutes [43]. However, the cost-benefit remains a subject of debate and depends on the baseline cure rate without IOPTH and the cost of the IOPTH system used. The principle of IOPTH is that the PTH will fall briskly in a hypercalcaemic patient following removal of the diseased gland due to the short half-life (5 min) of PTH and suppression of the normal parathyroid glands by hypercalcaemia [8]. The Miami criteria describe an intra-operative PTH fall of >50% at 10 min post-excision as compared to the highest pre-incision or pre-excision of hyperfunctioning parathyroid tissue to ensure cure [65]. The other algorithms followed include Vienna, Halle and Rome, but are less widely adopted [43]. Combining various IOPTH criteria can help increase surgical cure, however, most criteria were found to be unequal in predicting cure in multi-gland disease [43].

7. Re-Operative Parathyroidectomy

Patients not cured at first surgery require careful re-evaluation in a specialist center with experience in re-operative parathyroid surgery because of the increased risks associated with re-operative parathyroidectomy [66]. Confirmation of the diagnosis, use of genetic testing, review of the first-line imaging, surgery, and histology are fundamental prior to considering second-line imaging.

8. Benefits of Parathyroidectomy

Parathyroidectomy is associated with an improvement of 2–4% in bone mass in the first post-operative year after surgical cure and continues to improve thereafter [22]. This improvement is seen most rapidly in the hip and lumbar spine, followed by distal radius [59]. It also reduces the risk of hip and upper limb fractures, lowers the risk of stone formation, lowers urinary calcium excretion and appears to have a remarkable but incompletely understood improvement in subjective symptoms in most patients [3,22].

9. Post-Operative Management

Post-operative serum calcium levels should be assessed in the first 24 hours after surgery and monitored in case of symptomatic hypocalcaemia. Symptomatic post-operative hypoparathyroidism is uncommon and usually transient. It may be associated with pre-operative vitamin D deficiency, osteoporosis and high body mass index (BMI) (>40 kg/m^2). Post-operative hungry-bone syndrome is another cause of temporary hypocalcaemia and is usually seen between the 3rd and 5th post-operative day in younger patients or pregnant women. Hypoparathyroidism is characterised by normal or low PTH levels in relation to hypocalcaemia and normal or increased 24-hour urinary calcium excretion. Biochemistry in hungry bone syndrome

shows normal or elevated PTH levels and low 24-hour urinary calcium. Treatment with calcium supplements and vitamin D is recommended only if symptomatic and to have an adjusted serum calcium level >2.10 mmol/L. Intravenous calcium should be reserved for profound symptomatic hypocalcaemia (below 1.90 mmol/L) [67].

10. Complications of Parathyroid Surgery

Post-operative complications are rare after parathyroidectomy, especially in high-volume centres. The most important complications include haematoma, recurrent laryngeal nerve (RLN) injury, post-operative hypocalcaemia, and persistent or recurrent hyperparathyroidism. Permanent hypoparathyroidism is uncommon after focused parathyroidectomy; however, the risk may increase following bilateral neck exploration or re-operative surgery where normal parathyroid tissue is at greater risk of injury or devascularisation [68]. The risk of recurrent laryngeal nerve injury has been reported to range between 0.3% and 0.9% [69].

11. Future Perspectives

There is no proven alternative medical therapy for PHPT that can compete with a parathyroidectomy, so it is reserved for patients where surgery is not an option or is refused. Alendronate can help improve bone health; however, it does not help lower serum calcium levels or fracture risk. Cinacalcet (calcium sensor receptor modifying agent) and other calcimimetics help normalize serum calcium level; however, does not alter bone mineral density [70]. Knowledge of molecular mechanisms in the aetiopathogenesis of PHPT, assessment of bone microstructure using histology, and the use of artificial intelligence for data integration have resulted in a change in the approach to PHPT from one-size-fits-all to individualized precision therapy [71]. ^{18}F-Flurpiridaz and ^{18}F-(4-Fluorophenyl)triphenylphosphonium are newer molecules being investigated to improve identification of parathyroid adenomas [34].

12. Limitations of Current Evidence

There have been significant advances in the diagnosis and management of primary hyperparathyroidism; however, the current evidence is limited by retrospective studies, single-centre experiences, and observational cohorts, particularly regarding newer imaging modalities, artificial intelligence-based localization tools, minimally invasive approaches, and ablative therapies. Different criteria for patient selection, institutional imaging protocols, surgical expertise, and definitions of outcomes limit direct comparison between studies.

Evidence for advanced localization techniques such as ^{18}F-choline PET/CT and deep learning-based approaches continues to evolve. Machine learning models have their inherent vulnerability to bias from non-independent training and validation datasets, affecting their current clinical applicability. Treatment modalities such as robotic parathyroidectomy and thermal ablation require longer-term follow-up and comparative studies to establish their role relative to conventional focused and bilateral exploration approaches.

13. Conclusion

Primary hyperparathyroidism is now a relatively commonly diagnosed disorder. A comprehensive biochemical evaluation and early intervention can help prevent the progression to symptomatic disease and end-organ damage. Prevention of end-organ damage depends on early recognition, appropriate referral, and treatment. Localization of parathyroid disease facilitates targeted surgery, but non-localization of diseased parathyroids in a confirmed case of PHPT is not a contraindication for surgery in a center familiar with this scenario. Surgery is currently the only definitive treatment for PHPT. Observation and medical management are less cost-effective and less efficacious than surgery in preventing the long-term deleterious effects of PHPT in both symptomatic and asymptomatic cases. Recurrent PHPT is best managed in specialized centers where a thorough review of previous imaging, surgical and histopathological details is required, followed usually by second-line imaging if indicated before re-operative parathyroid surgery.

Key Points

• PHPT is now one of the most common endocrine disorders worldwide, with a higher incidence in post-menopausal women.

• It may present with classic symptoms such as bone loss and kidney stones, but many patients in high-income countries are diagnosed with asymptomatic forms of the disease.

• Surgery is the definitive treatment for PHPT and should be offered to all symptomatic patients and also in asymptomatic patients <50 years, serum calcium >1 mg/dL (0.25 mmol/L) above the normal range and/or with evidence of end-organ damage.

• Minimally invasive and focused parathyroid surgery, aided by pre-operative imaging techniques and use of IOPTH, is increasingly being used for PHPT and improves the chances of cure.

• Parathyroidectomy leads to improvements in bone mass and reduces the risk of fractures, kidney stone formation, and other complications associated with PHPT.

• Rarely, patients may have persistent or recurrent disease, necessitating re-confirmation of biochemistry, consideration for genetic testing, re-imaging to localise the lesion and referral to centres experienced in re-operative parathyroid surgery.

Availability of Data and Materials

The data that support the findings of this review are available from the corresponding author upon request.

Author Contributions

Drafting, conception and design—ST; conception and design—FFP. Both authors contributed to revising the manuscript critically for important intellectual content. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This review was performed in accordance with the Declaration of Helsinki. Consent has been obtained from patients for incorporating the images.

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Conflicts of Interest

The authors declare no conflicts of interest.

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