AME Position Statement: Primary hyperparathyroidism in clinical practice

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INTRODUCTION

Why this document

The epidemiological and clinical profiles of primary hyperparathyroidism (PHPT) have changed markedly over the past few decades. PHPT is now one of the most frequent endocrine disorders in clinical practice, with prevalence increasing with age. The clinical presentation of PHPT has progressively shifted from the classic form, with kidney stones, overt bone disease, and marked hypercalcemia, to a nearly or completely asymptomatic disease. Finally a *fruste form* of PHPT, normocalcemic hyperparathyroidism (NCPHPT), is increasingly encountered with its diagnostic and therapeutic challenges.

The general consensus is that most patients with symptomatic PHPT, if surgery is not contraindicated owing to comorbidities, should be referred for parathyroidectomy (PTX), which remains the only curative treatment. On the other hand, the indication for PTX in asymptomatic and often clinically stable patients still remains controversial. Emerging evidence supports PTX even in asymptomatic patients owing to advances in effectiveness and safety of surgical procedures.

The effectiveness of surgery is matched by new data on the efficacy of medical therapies, such as bisphosphonates and calcimimetics on disease-specific indices such as bone mineral density (BMD) and serum calcium, respectively, and thus may represent a reasonable alternative for patients who cannot undergo or refuse surgery.

Currently, PHPT is one of the leading reasons for seeking endocrine consultation but still raises challenging questions for both the physicians and their patients. Accordingly, the Italian Association of Clinical Endocrinologists (AME) considered timely and appropriate to assemble a panel of Italian experts with the task of drafting a Position Statement about clinical management of PHPT.

Methodology

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system was adopted for the present Position Statement (1-4). Briefly, the GRADE system classifies evidence into four quality levels (high, moderate, low, very low), and recommendations into two grades (strong or weak). The wording "we recommend" is used for strong recommendations, whereas "we suggest" denotes weak recommendations. The strength of recommendations is not necessarily, although it is in most cases, related to the levels of evidence. The strength of the recommendations may be upgraded or downgraded by a number of other factors.

For example, inconsistency of results, indirectness of evidence, lack of precision and limited number of relevant publications downgrade a recommendation. On the other hand, a large effect size may upgrade a recommendation (3).
We have indicated as "recommendations" the strong recommendations and as "suggestions" the weak recommendations. Each recommendation is based on quality of supporting evidence, downgrading or upgrading factors, and the level of agreement between the panel members.
Whenever possible, the level of evidence (LoE) has been reported beside each quotation using the following symbols: very low (⊗○○○), low (⊗⊗○○), moderate (⊗⊗⊗○), and high (⊗⊗⊗⊗) quality. Briefly, "very low quality" evidence are the unsystematic clinical observations (case report, case series) or very indirect evidence (i.e. surrogate endpoints); "low quality" evidence is from observational studies or randomized controlled trial (RCT) with major limits; "moderate quality evidence" derives from RCT with important limitations or from rigorous observational studies; "high quality evidence" are well-performed RCT and, exceptionally, strong evidence from unbiased observational studies (3).

GENERAL ISSUES

Epidemiology

Incidence, even though drawn from small series, was reportedly 15-20 cases/100,000/yr, with age peak at 65-75 yr, and prevalence was 0.1-0.4%, rising to 2% in women older than 55 yr (5, 6).
PHPT occurs more frequently in women (F), mostly after menopause, than men (M): the ratio F:M is 3:1, increasing to 5:1 in elderly European patients (5, 6).

Classification

The sporadic PHPT is the most frequent (95% of cases); hereditary forms are rare (<5%) and include: multiple endocrine neoplasm (MEN) 1 and 2a, hyperparathyroidism-jaw tumor syndrome (HPT-JT), familial isolated PHPT (FIHPT), and neonatal PHPT.
A single parathyroid adenoma is responsible for approximately 80-85% of cases of PHPT; in the remaining patients PHPT can be ascribed to multiple adenomas or hyperplasia of all the glands. Parathyroid cancer is very rare (<0.5%).
The "symptomatic" PHPT, heralded by kidney stones, overt bone disease, and marked hypercalcemia, is currently less common than the asymptomatic form. Even though classic manifestations of the disease are lacking, "asymptomatic" patients frequently present with osteopenia or osteoporosis, as well as "non-traditional" manifestations, such as cardiovascular (CV) and neurocognitive abnormalities.
Recently, a new clinical entity, NCPHPT, has been identified but little is known about its natural history, potential complications, and most appropriate management.
Very rarely PHPT may occur during pregnancy, in the newborn or as hypercalcemic crisis (acute hyperparathyroidism).

Natural history

In symptomatic patients, the benefits of PTX on the classical and non-classical complications of the disease and on the risk of CV mortality are well documented.
Many patients with asymptomatic PHPT who are followed conservatively remain asymptomatic for a long time; clinical progression occurs in 23-62% at 10 yr (7). In asymptomatic PHPT, however, surgical cure leads to a prompt increase of BMD. Finally, despite some evidence on the association of asymptomatic PHPT with CV and neuropsychological manifestations, a clinically significant improvement of these symptoms after surgery is still an area of controversy.

DIAGNOSIS

Biochemical assessment of PHPT

The diagnosis of PHPT relies on the demonstration of hypercalcemia with the concomitant finding of elevated or inappropriately normal PTH concentrations (8).
The total serum calcium concentration should be used for both the initial and the repeated measurements (9). If abnormalities in serum albumin concentrations are suspected, calcium values should be corrected for the abnormality in albumin using the following formula (calcium measured in mg/dl and albumin in g/dl):
measured serum calcium + [0.8 × (4 – measured albumin)].
If a reliable method is available, a direct measurement of the ionized calcium is advisable (8).
The measurement of intact PTH (1-84) molecule by a two-site immunometric assay of at least second generation is the preferred method of PTH measurement (8).
The serum phosphorus is reduced in approximately 25% of patients with PHPT (9); hence the sensitivity of its measurement for the diagnosis of PHPT is low.
25-Hydroxyvitamin D (25-OH-D) should be measured in all patients with PHPT: 25-OH-D levels in

the range of deficiency (i.e. <20 ng/ml) (10, 11) were found in 27 to 53% of these patients (12-15). When a deficiency of 25-OH-D is confirmed, then a period of treatment with vitamin D should ensue (8).

We recommend the concomitant determination of total serum calcium and PTH to confirm the diagnosis of PHPT. Correction for serum albumin is recommended.

We suggest using ionized calcium determination when a reliable assay is available.

We recommend evaluation of 25-OH-D status in all patients with PHPT, in order to provide supplementation if deficiency is found.

Differential diagnosis

A chronic asymptomatic hypercalcemia is suggestive of PHPT, but the much less common possibility of benign familial hypocalciuric hypercalcemia (FHH) should be ruled out (16). Urinary calcium excretion (UCa) is normal or increased in patients with PHPT (7). The ratio of calcium clearance to creatinine clearance (measured in mg/dl either on a 24-h or on a spot urinary collection) has been suggested after the adequate repletion of vitamin D for separating patients with FHH from those with PHPT: the ratio is, respectively, lower and higher than 0.010 (17, 18).

CLINICAL PRESENTATION AND EVALUATION OF ORGAN DAMAGE

Symptomatic PHPT

Renal disease

The two main clinical renal manifestations of PHPT are nephrolithiasis and nephrocalcinosis. Nephrolithiasis occurs in 20-40% of PHPT patients (in previous series before the eighties even 60%), and it can present as asymptomatic in about 7% of patients with PHPT (19). Hypercalciuria, higher oxalate excretion, and severe PHPT are associated with kidney stones (20, 21). The risk of renal stone disease decreases following PTX, up to normalization after 10 yr (22).

Nephrocalcinosis is rarely reported in PHPT patients (3%). Risk factors are unknown and the effect of PTX is negligible (8, 21).

The occurrence of nephrolithiasis or nephrocalcinosis has a significant impact in the therapeutic strategy.

A reduction in glomerular filtration rate (GFR) is frequent in PHPT, as a consequence of nephrolithiasis, nephrocalcinosis, or severe hypercalcemia. The prevalence and severity of renal insufficiency vary considerably, with recent studies in PHPT reporting a 20-30% prevalence, including mild forms (23, 24). The decline of renal function, even mild (24), may worsen features of PHPT (hypertension, frequency of diabetes, and bone alterations) even in asymptomatic patients (25, 26).

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines recommended the estimation of GFR through the modification of diet in renal disease (MDRD) equation or the Cockroft-Gault equation (27). GFR at 60 ml/min defines a threshold below which surgery is recommended in asymptomatic PHPT (28).

For the evaluation of renal damage, serum creatinine and GFR are cost-effective and thus mandatory. As for imaging, ultrasonography (US) has become very popular, owing to many advantages, including low cost, widespread availability, and absence of radiation. US has limited specificity for the detection of renal calculi because of confusion related to small stones and arcuate arteries, and can image only the kidney and the proximal ureter. However, US may detect silent kidney stones (29) and its routine use appears suitable in PHPT patients (8, 28, 30-32).

We recommend serum creatinine and estimated GFR evaluation.

We suggest routine use of kidney US in patients with PHPT.

Bone disease

Cortical resorption is typical and an increased rate of vertebral fractures has been reported in several studies. However, all studies were retrospective or limited by several biases (33). Recently, two case-control studies (34, 35) remarked higher vertebral fracture risk in patients with PHPT (most fractures were mild), positively correlated with the severity of PHPT and the degree of BMD decrease.

Osteitis fibrosa cystica (OFC), with bone cysts, osteoporosis, and brown tumors, is the classic skeletal manifestation of severe PHPT, with any bone potentially affected as the disease progresses. OFC is seldom observed nowadays (36).

Evaluation of bone damage. The most common radiographic finding is decreased bone density but unfortunately it is non-specific. Conventional radiography can evidence soft tissue calcifications in the joints and kidneys (37), but no specific radiographic change is observed in most patients with PHPT. When present, sub-periosteal bone resorption that can be seen on conventional X-rays of the hands is diagnostic.

Spine X-ray examination is the gold standard to detect vertebral fractures. Vertebral morphometry is a semi-quantitative method to identify osteoporotic vertebral fractures. It relies on the computation of

relative changes when measuring different vertebral heights (38).
Dual-energy X-ray absorptiometry has become the gold standard in the assessment of skeletal involvement in PHPT (39). Most studies point to PTH as a catabolic factor at cortical sites: BMD is indeed reduced at the distal radius while the lumbar spine is relatively well preserved. The hip region, containing a relatively equal admixture of cortical and cancellous elements, shows BMD that is intermediate between axial (spine) and appendicular (radius) sites (40, 41).
Several studies in patients with PHPT revealed that successful surgery leads to sustained increases in BMD at lumbar spine and hip.
BMD measurement is thus advisable at all sites for the evaluation of most involved skeletal sites at diagnosis and to evaluate recovery after treatment.
PTX is very efficacious also in patients affected by OFC, achieving higher increases in BMD at 3-4 yr after surgery (42, 43). However, PTX and medical anti-resorptive treatment were equally effective in increasing BMD at 3 yr (44, 45).

We recommend against skeletal X-ray as routine examination in PHPT.
We recommend BMD measurement at diagnosis and at 1-2-yr intervals in individuals with PHPT who do not undergo surgery (for follow-up after PTX see below).
We suggest looking for vertebral fractures by vertebral morphometry in PHPT patients with osteoporosis or related symptoms.

CV and metabolic involvement

The CV manifestations of PHPT are still being debated or controversial. In older series of symptomatic patients, CV mortality was reportedly increased, but in less symptomatic patients CV involvement is controversial: an increased CV mortality was found in some retrospective European studies (46-48) but not confirmed in an American study (49). Curative surgery had positive effects on hard CV endpoints in symptomatic PHPT (47) but not in mild PHPT (50).
Hypertension is frequent in PHPT, but the lack of a known pathophysiologic linkage and the erratic inconsistent response (increase, decrease, and no change) to PTX in retrospective small series (51-53) cannot rule out a possible selection bias due to the relatively high prevalence of both PHPT and hypertension in the general population.
No data are available about the risk of coronary artery disease in patients with PHPT.
Myocardial and valvular calcifications were reported in symptomatic PHPT patients with marked hypercalcemia (54), but not in those with mild PHPT and lower serum calcium (55).
Increased left ventricular mass, a predictor of CV mortality, was found in PHPT in some studies (56, 57): its decrease after surgery was observed in some small series of patients with a short follow-up (56, 57).
Abnormalities of vascular system and of cardiac function such as diastolic dysfunction were evaluated without significant results in PHPT: increased arterial stiffness, endothelial dysfunction and carotid plaques were described in small series (58, 59). Technical difficulty and limits in the reproducibility of these measurements reduce the clinical implications of these findings.
Higher frequency of impaired glucose tolerance, Type 2 diabetes, dyslipidemia, gout, and increased body weight have been reported in PHPT together with increased insulin resistance (46, 60, 61). Overall, these metabolic alterations have been found to improve after surgical cure of PHPT, as well as CV morbidity and mortality (46).

We suggest evaluating for CV involvement by measuring arterial blood pressure, stratifying the CV risk factors at diagnosis and after curative surgery for PHPT. Other measurements cannot be recommended for routine use.

Neurological, psychiatric, and cognitive symptoms

Non-specific neuropsychiatric manifestations, such as anxiety, cognitive difficulties, and somatic complaints, may be found in symptomatic PHPT patients (62), but their recovery after PTX could not be predicted.
Moreover, classical PHPT was found to be associated with a distinct neuromuscular syndrome characterized by mostly Type 2-muscle cell atrophy leading to easy fatigability, symmetric proximal muscle weakness, and muscle atrophy (63, 64). An improvement in muscle function was reported after PTX in most of the few studies focusing on this topic (63, 64).
Psychological symptoms or complaints [depression, anxiety, or poor quality of life (QOL)] were investigated mainly in observational studies, with reported improvements after PTX (65). However, RCT in mild PHPT yielded contradictory results (66-68).

We suggest against routine formal testing for neurological, psychiatric, and cognitive symptoms, but it might be useful in some selected cases.

Other complications

These are nowadays seldom reported.
Gastrointestinal complaints, such as constipation, nausea, vomiting, and abdominal pain due to large

bowel and gastric atony, have been associated to hypercalcemia in PHPT (69). In some PHPT cases, abdominal pain, nausea, and vomiting have been related to peptic ulcer disease or pancreatitis (69). Elevated serum calcium levels leading to a reduction in neuromuscular excitability and hypergastrinemia as well as deposition of calculi within the pancreatic ductules have been proposed as pathogenic factors of peptic ulcer disease and pancreatitis, respectively, in PHPT (69). After surgical cure of PHPT peptic ulcers or ulcer symptoms may or may not resolve, but variable improvement of pancreatitis has been reported (69).

Asymptomatic PHPT

This is currently the most frequent form of presentation of PHPT and is characterized by the absence of classical manifestations of the disease. Nevertheless non-specific alterations that pertain both to classical and non-classical target organs are described (53, 60, 61, 67, 68, 70).

Most asymptomatic PHPT patients have reduced BMD (53, 67, 68, 70). RCT have demonstrated improvement in BMD at the hip and lumbar spine regions at 1 or 2 yr after PTX, without any significant effect on cortical bone sites, such as the radius (53, 67, 68, 70). Also a long-term follow-up study after surgery confirmed an increase in lumbar and femoral neck BMD, without benefit at the radius (71). On the other hand, many studies have established that there is no clear progression of bone disease if PTX is not performed (53, 67, 68, 70-72). In fact, in short-term RCT, conservatively managed patients demonstrated stable BMD at both the radius and lumbar spine sites while there was a small but statistically significant decrease in total hip over 1-yr follow-up (67, 68, 70). In a long-term follow-up study, BMD was stable in 79% while progressing in 21% of PHPT patients (71). A recent metanalysis confirmed that untreated mild PHPT is not associated with continued accelerated bone loss at any of the measured skeletal sites (73). In asymptomatic PHPT there is evidence supporting an increased fracture risk (74), while still lacking definitive evidence that PTX reduces this risk.

CV alterations are also reported in asymptomatic PHPT (63). Whether this finding could increase CV morbidity and mortality in mild PHPT is still matter of debate (11, 48, 49, 75). Conclusive evidence of amelioration in these alterations after PTX is still lacking.

Most patients with PHPT suffer from non-specific psychiatric and cognitive symptoms (fatigue, lassitude, mood swings, irritability, anxiety, depression, difficulty in concentrating, and memory loss) that affect their QOL (64). Overall, there is a growing body of evidence, though still not conclusive, showing an improvement in QOL after curative PTX (67, 68, 70).

All our previous suggestions and recommendations about symptomatic disease apply also to asymptomatic patients.

Normocalcemic PHPT

The diagnosis of NCPHPT can be made in subjects with persistently normal serum total and ionized calcium but with elevated PTH levels, in whom secondary causes for an elevated PTH have been excluded (76, 77). The most common cause of secondary hyperparathyroidism is vitamin D deficiency. After correcting vitamin D deficiency with supplementation and excluding other causes of secondary hyperparathyroidism (77), such as hypercalciuria, reduced creatinine clearance (<60 ml/min), malabsorption, bisphosphonates, anticonvulsants, and loop diuretics (furosemide), the persistence of normal calcium levels in the face of high serum PTH makes it possible to diagnose NCPHPT.

The epidemiology of NCPHPT is still uncertain, with prevalence ranging from 3 up to 20% (78, 79).

Different theories tried to explain the pathogenesis of NCPHPT, from precocious subclinical phase of PHPT, followed later by a clinical stage when hypercalcemia becomes overtly manifest, to a generalized resistance to PTH at target tissues (76, 80, 81). NCPHPT has also been hypothesized as the earliest form of symptomatic rather than asymptomatic disease (76).

The natural history indicates that about 20% of patients with NCPHPT will progress to overt hypercalcemic illness throughout the years. However, progression to hypercalcemia is not inevitable nor is there any uniform time course for its development (76, 81-83).

The treatment of NCPHPT is yet to be defined, therefore, guidelines for the management of asymptomatic PHPT (82) cannot be applied with confidence to NCPHPT.

Familial forms

Familial forms account for 5% of PHPT cases (84). A mutated gene was definitely linked to the disease in three syndromes (Table 1) (85-87).

Table 1 - *Familial forms of primary hyperparathyroidism.*

Disease	Mutated gene
MEN 1	*MEN1* (85)
MEN 2a	*RET* (86)
HPT-JT	*HPRT2* (87)

Other mutations were identified rarely in other genes (88) and some cases of FIHPT are still awaiting the identification of mutated genes (89).
MEN 1 is an autosomal dominant disease involving different endocrine organs, mainly parathyroid glands (>90%), pancreas (40%), and pituitary (20%), due to an inactivating mutation of *MEN1*, a tumor suppressor gene. Other organs may be also affected: adrenals, thymus, lungs, and skin. PHPT in MEN 1 occurs in twenties (about 30 yr earlier than in the sporadic form), without gender difference, with an asymptomatic clinical course for years, until fifties when over 90% of carriers is clinically affected. It was suggested to suspect MEN 1 if PHPT occurs before 50 yr and PTH values are in the normal range (90). In these latter patients the ratio of calcium clearance to creatinine clearance should be measured (in order to exclude FHH), as well as the other serum hormones that can be more frequently increased in MEN 1 (i.e. PRL, gastrin).
MEN 2a is an autosomal dominant disease due to an activating mutation of the *RET* oncogene, identified in over 90% of familial forms. Clinical picture include medullary thyroid carcinoma (95%), pheochromocytoma (50%), and PHPT (30%). In this syndrome PHPT is commonly asymptomatic, with median age of 38 yr at presentation (91).
HPT-JT is a rare autosomal dominant disease due to an inactivating mutation of *HPRT2*, a tumor suppressor gene coding for parafibromin, encompassing parathyroid asynchronous neoplasms (carcinoma in 15%), ossifying tumors of jaws (30%), kidney tumors (15%, Wilm's tumors, cysts, amarthomas), and uterine fibromyomas. Other abdominal organs may be involved too (92).
FIHPT are autosomal dominant diseases affecting one or more parathyroid glands, without involvement of the other endocrine glands seen in MEN syndromes.
FHH is an important differential diagnosis. This is an autosomal dominant disease due to an inactivating mutation of the *CaSR* gene (93). This mutation induces a right shift of the calcium-PTH set-point at the parathyroid cell level as well as an increase in renal tubular calcium reabsorption. FHH is not an indication for PTX and persisting hypercalcemia after PTX should raise the suspicion of FHH. FHH is to be ruled out in subjects with hypercalcemia and hypocalciuria after ruling out drug interference (lithium and thiazide diuretics above all) even when family history of hypercalcemia is negative.

Use of genetic tests

These tests, aiming to identify carriers in patients with known or suspected genetic disease, can:

- confirm diagnosis in the proband;
- confirm diagnosis in proband's relatives with little or no symptoms;
- rule out diagnosis in proband's relatives at risk.

Furthermore, genotyping in some familial forms impacts on therapeutic choices (i.e. MEN 2) and follow-up (i.e. FHH, HPT-JT) (8, 94).
Genetic tests are not able to identify all mutations causing disease (94), owing to:

- sequence alterations in not analyzed regions (regulatory regions, introns);
- large deletions not detected by sequence analysis;
- occurrence of mutation in a different gene.

Failure to identify mutation in a proband is more frequent in sporadic than in familial forms and depends on the evaluated gene (i.e. MEN 1 20-30% *vs* MEN 2a 10%) (94, 95).
Mutations of *MEN 1* gene are identified in 70% of familial forms (where tumors occurs in proband and in one first-degree relative bearing a major neoplasm of the syndrome) and in 7% of sporadic cases (84). Genotyping is indicated to confirm clinical diagnosis (even in atypical cases) and to identify carriers. Familial screening is to be performed in the first decade (94).
It is well-known the strict relationship between genotype and phenotype in MEN 2a, with PHPT more often associated to mutations in codon 634. Screening for mutations in *RET* is crucial to stratify the risk for medullary thyroid carcinoma (94).
Mutations in *HRPT2* were identified in 70% of HPT-JT (87), in parathyroid carcinomas (germline in $^1/_3$), and in some families previously diagnosed as FIHPT. In view of high prevalence of parathyroid carcinomas in carriers of germline mutations of *HPRT2*, their identification is useful for clinical surveillance and early treatment (96).
Genetic background of FIHPT is unknown: more than 20% of them are reclassified after identification of a mutation in *CaSR*, *MEN 1*, or *HRPT2* (89).
FHH represents one main application of genetic testing, because PTX is not indicated, whereas homozygotes have severe neonatal PHPT and require total PTX within a few weeks from birth. The analysis must be performed in patients with hypercalcemia with relative hypocalciuria (calcium clearance/creatinine clearance <0.01) (17) and familial hypercalcemia, as well as in patients with persisting hypercalcemia after PTX. Disappointingly, no mutation was identified in 30% of patients with clinical suspicion of FHH (97).

We suggest referral of patients with familial forms to tertiary level centers.
We recommend searching for mutation in *MEN 1*

to confirm clinical diagnosis (even in atypical cases) and to identify carriers (in the first decade).
We suggest searching for mutation in *HPRT2* in familial forms of PHPT not due to *MEN 1* mutations or in presence of parathyroid carcinoma.
We suggest searching for mutations of *CaSR* gene in patients with biochemical findings suggestive for FHH or when screening of the familial forms of PHPT is inconclusive and also in newborns with severe hypercalcemia.

Other presentations

Hypercalcemic crisis

Hypercalcemic crisis due to PHPT is a life-threatening condition that is currently rarely seen (98). It has been associated with higher serum calcium (≥14 mg/dl) and PTH levels, larger parathyroid glands and higher incidence of parathyroid carcinoma than in PHPT without hypercalcemic crisis. Most common symptoms are mental status changes, including somnolence and coma, as well as weakness, nausea, vomiting, polyuria, dehydration followed by oligo-anuria, and increased risk of arrhythmia and pancreatitis (98). This condition should be promptly recognized and treated.
Evaluation. The most important diagnostic clue is the elevation of serum PTH levels that discriminates from hypercalcemia of malignancy.

PHPT in pregnancy

PHPT is a rare presentation in pregnancy (99, 100). However, PHPT must be taken into account since it could have serious complications on both the mother and fetus/newborn if it goes undiagnosed, in both symptomatic and asymptomatic forms (99, 100). Maternal complications of PHPT (up to 67% of cases) involve nephrolithiasis, bone disease, gastrointestinal complaints, hypertension, pre-/eclampsia, hypercalcemic crisis, polyhydramnios, miscarriage (99, 100). Fetal and neonatal complications of PHPT (up to 80% of cases) include intrauterine fetal demise, pre-term delivery, low birth weight, neonatal hypocalcemia with tetany, and neonatal death (99, 100).
Serum calcium levels corrected for serum albumin levels or ionized calcium should be assessed before and during pregnancy, particularly in women with a history of miscarriage, and hypercalcemia thoroughly investigated and treated (99, 100).

PROCEDURES FOR LOCALIZATION

Imaging studies have no role in the diagnosis of PHPT. They should be taken into account for preoperative localization to plan the operative approach when PHPT diagnosis has been established by biochemistry. Unfortunately, imaging studies may yield false positives and in case of visualization of a single image suggestive for parathyroid adenoma, a multiglandular disease cannot be ruled out (101).

First-line

Scintigraphy

Scintigraphy is an accurate non-invasive procedure for the localization of parathyroid adenomas in both eutopic and ectopic sites (102-105). A sensitivity of 84.5-98% and a specificity of 60-95.7% have been reported (106, 107).
A specific tracer for parathyroid tissue does not exist. The most utilized is ^{99m}Tc-2-methoxy-isobutyl-isonitryl (SestaMIBI) that is taken up by the thyroid tissue as well. Sensitivity of SestaMIBI scintiscan may be reduced in cases of multiglandular disease, small size (<5 mm) parathyroid adenomas, chief-cells histology, low proliferation index and/or functional activity of the adenoma (108-111). On the other hand, concomitant thyroid disease, such as hyperfunctioning adenoma or neoplastic nodule, is a major cause of false positive scintigraphic results (112).
The recent development of integrated single photon emission computed tomography (SPECT)/computed tomography (CT) systems, combining gamma-camera and CT in the same gantry, provides an optimal fusion of metabolic (SPECT) and anatomic (CT) images, further improving accuracy in ectopic parathyroid adenomas and when neck anatomy is distorted (113).

US

High-resolution US is a first-line tool for localizing parathyroid adenoma in patients with PHPT (101-104, 114-116). Even though US is operator-dependent and does not provide any functional information, it offers detailed information about parathyroid adenoma size, structure and anatomic relationship with contiguous neck structures, offering the highest accuracy for correct quadrant localization. Accordingly, US has been proposed as the single best imaging technique for surgical planning in mini-invasive, focused surgery (116-119).
Sensitivity and specificity of US range widely (55-90%), both being affected by the skill of the examiner, the occurrence of ectopic adenomas, the rate of multiglandular disease, and the coexistence of multinodular goiter (102, 104, 115). Furthermore, central neck compartment lymph nodes, chronic autoimmune thyroiditis pseudonodules and other neck masses may be misdiagnosed as enlarged parathyroid gland (102, 115).

Occasionally, the suspicion of parathyroid carcinoma may be raised by non-specific findings (e.g. large lesions with irregular and ill-defined margins, infiltrating other neck structures) (115).

US *vs* scintigraphy

US and scintigraphy have proven to be equally effective as first-line tools for parathyroid localization. It is generally acknowledged that the combination of US and scintigraphy maximizes the likelihood of a correct localization (102, 104, 105, 120). As compared to scintigraphy, US offers the advantages of lower costs without patient exposure to radiation. More important, US is an anatomic imaging technique, offering a more accurate localization of the correct quadrant and side (121, 122), as well as detailed information about thyroid size and nodules, lymph nodes, and other neck structures (102, 115). SestaMIBI scintigraphy is more sensitive in the localization of ectopic adenomas (102-105, 123).

Taking into account that imaging procedures are not to be used for diagnostic purposes, **we recommend** performing imaging in all biochemically confirmed PHPT, with the combined use of US and scintigraphy (possibly completed by SPECT) as first line.

We recommend that all patients referred to parathyroid surgery undergo neck US because a detailed evaluation of thyroid gland as well as of cervical lymph nodes is required.

Second-line

Magnetic resonance imaging and CT

Due to the accuracy of the first-line imaging studies, the use of magnetic resonance imaging (MRI) and CT in localization of parathyroid adenomas is quite limited (101-105, 116). Nevertheless, in the few available series, sensitivity and specificity of both techniques are reportedly comparable to those of scintigraphy (124-128).

CT and MRI are usually adopted in the following settings: a) detailed visualization of a parathyroid adenoma suggested by an ectopic (e.g. mediastinal) uptake at SestaMIBI scintiscan; b) planning of second surgery in patients with PHPT persistence. They can be optionally used in patients with complete negativity of the first-line imaging studies or discrepancy in their results.

Parathyroid fine-needle aspiration biopsy

Parathyroid fine-needle aspiration biopsy (FNAB) completed by intra-lesional PTH measurement has proven to be an accurate technique for confirming US localization in case of discrepant US and scintigraphy results or ambiguous US findings, especially in patients undergoing re-operation (102, 106, 115, 129-134). Furthermore, it could play a role in pregnant women, where scintiscan cannot be employed. In experienced hands, this technique seems to be safe and devoid of relevant side effects (106, 131-135). Caution against FNAB is advisable when parathyroid carcinoma is suspected, as seeding of cancer cells along fine needle track has been anecdotally reported (136, 137). Besides, FNAB may induce fibrotic changes causing some problems in the histological evaluation of parathyroid lesions (138, 139).

Fluorodeoxyglucose-positron emission tomography

The role of positron emission tomography (PET) and PET/CT in the evaluation of PHPT is still to be defined. Available results are promising yet still controversial, and limited by the small series studied. Identification of parathyroid adenomas not localized by other imaging techniques with ^{18}F-fluorodeoxyglucose (FDG)-PET has been reported (140, 141); however, on a routine basis, ^{18}F-FDG-PET findings are difficult to be interpreted due to normal anatomic variants or benign uptake in neck region (brown fat, salivary glands, thyroid, inflammatory lymph nodes).

^{11}C-Methionine and ^{18}F-DOPA seem promising tracers but the experience is still quite limited (142-144).

In conclusion, at present PET and PET/CT cannot be recommended as routine localization procedures in patients with PHPT and should be reserved to selected cases, especially in patients previously operated on.

Selective angiography or selective venous sampling can be employed as third-line in selected cases in patients undergoing re-operation.

We recommend MRI and/or CT when an ectopic parathyroid adenoma is suspected.

We recommend MRI and/or CT when both US and scintigraphy are not conclusive in patients undergoing second surgery.

We recommend parathyroid FNAB with intralesional PTH measurement as a second-line technique in case of ambiguous and/or discrepant US and scintigraphy findings.

TREATMENT

Why and how

Aim of the treatment is normalizing serum calcium and PTH, and reverting to normal the risk of comorbidities associated to PHPT. When PHPT is effectively cured, most of its clinical consequences

usually regress. Observational studies demonstrate that effective PTX is followed by improvement in BMD, and reduction in fracture rate and kidney stone frequency. The data addressing neurocognitive symptoms are less solid, and little is known about the CV profile of PHPT, but both these aspects could be positively influenced by PTX (145).

Indications to surgery

There is a general agreement that surgery is the first-line treatment for all patients with symptomatic PHTP, unless surgery is strongly contraindicated, because it is the only curative treatment. The vast majority of patients will be cured by PTX if surgery is performed by a skilled surgeon. The expected benefit is large in patients with gross bone involvement (osteoporosis, PTH-related bone focal lesions), severe hypercalcemia or hypercalcemic crisis, and clinically relevant kidney stones.

Open issues

A long-standing debate is still ongoing about the asymptomatic forms of PHPT, specifically addressed by the 2008 Third International Workshop on Asymptomatic Primary Hyperparathyroidism. Surgery should be considered as definitive cure also in this case, but asymptomatic patients should be selected for surgery primarily on the basis of the severity of disease. The 2008 Workshop (82) indicates surgery is appropriate to be considered in all patients and should be recommended for the following asymptomatic PHPT patients:

- hypercalcemia more than 1 mg/dl above the upper limits of normal

or

- creatinine clearance <60 ml/min

or

- post-menopausal women and men >50 yr with T-score ≤2.5 SD at any site or previous fragility fracture; pre-menopausal women and men <50 yr with Z-score ≤2.5 SD (lumbar spine, femoral neck, total hip, or radius)

or

- age <50 yr.

The pre-operative localization of parathyroid adenoma has become a routine procedure. A successful pre-operative imaging localization is a strong factor, which plays a role in addressing the patient to surgical procedure even when clinical severity of PHPT is relatively low or in an asymptomatic patient. Even though drugs may ameliorate bone disease and control hypercalcemia, only surgery may ensure the normalization of the whole spectrum of clinical manifestations associated with PHPT, even in its mild "asymptomatic" form. It has been demonstrated that a positive preoperative scintigraphy increases the surgical cure rate of PHPT from 92.7% to 99.3% (146). Furthermore, pre-operative localization of parathyroid gland abnormalities allows patients to undergo unilateral neck exploration (UNE), as opposed to bilateral neck exploration (BNE), so potentially decreasing operative times, duration of hospitalization, and patient morbidity (147). On the opposite, a negative pre-operative imaging localization increases the risk of unsuccessful surgery (148). Comparing cure rate in 499 consecutive patients with negative and positive pre-operative localization, Harari et al. (149) demonstrated that the formers a) had lower cure rate; b) required more frozen sections; c) required longer surgical time; and d) were more likely to require BNE. They concluded that PHPT patients without pre-operative adenoma localization are more complex patients, requiring referral to highly experienced surgical teams in order to obtain higher success rate. The extent of surgery required by these patients is wider than in patients with positive localization, resulting more frequently in partial thyroidectomy, partial thymectomy, surgical re-exploration, or other extensive surgical procedures (150). Accordingly, the therapeutic decision-making process is based on the balanced evaluation of all the following issues: 1) severity of PHPT, 2) patient's clinical assessment and values, and 3) the outcome of pre-operative localization.

We recommend surgery in:

- patients with symptomatic PHPT;
- patients with asymptomatic disease addressing one or more of the criteria indicated by the 2008 Workshop on asymptomatic PHPT.

We suggest surgery also in patients with asymptomatic disease addressing none of the criteria indicated by the 2008 Workshop on asymptomatic PHPT, if pre-operative parathyroid adenoma localization is positive by first-line imaging studies and if a skilled surgeon is available.

We suggest conservative treatment in patients with asymptomatic disease addressing none of the criteria indicated by the 2008 Workshop on asymptomatic PHPT, if pre-operative parathyroid adenoma localization is negative by first-line imaging studies.

Surgery

PTX is the only treatment able to cure PHPT by removing all hyperfunctioning tissue.

Techniques and intra-operative PTH assay

Available surgical approaches are:

- BNE, allowing the inspection of all parathyroid

glands with the excision of those looking pathological. In hyperplasia, involving by definition all the glands, available options are subtotal PTX (i.e. ablation of 3 glands and ¾ of the fourth) and total PTX combined with auto-transplantation (some parathyroid fragments are implanted into a forearm muscle).
- UNE, allowing the excision of the previously identified adenoma with the concomitant inspection of the ipsilateral gland.
- Minimally Invasive Parathyroidectomy (MIP) is the focused and selective removal of the previously identified adenoma. MIP can be performed by a little cutaneous cut (MIP-open), by optical fibers (MIVAP), or by a probe catching the radioactivity previously accumulated in parathyroid glands (MIRP).

MIP and UNE must be performed only after successful pre-operative localization.
MIP can be performed during loco-regional anesthesia, achieving lower post-operative pain as compared to narcosis (151).
Intra-operative PTH assay (ioPTH) aims to assess cure (i.e. resection of all hyperfunctioning tissue) by evaluating hormonal fall during surgery. Several studies addressed this topic, but few were controlled and very few randomized (152). Different protocols for sampling times and cut-offs for cure were proposed. The best balanced protocol was agreed on in Miami-criterion (153): a fall in PTH greater than 50% from the highest of either the pre-incision or the pre-excision level at 10 min after gland excision is highly predictive of cure. This test is very reliable in uniglandular disease, whereas in multiglandular disease a more restrictive cut-off is advocated (i.e. PTH fall greater than 70%).

Since ioPTH would be an useful tool to confirm successful surgery in all patients submitted to PTX, **we recommend** performing ioPTH during MIP/UNE:
- when pre-operative localization by scintiscan and US is doubtful or discordant
- when pre-operative localization is based on a single study
- during repetitive surgery.

Extent of surgery and results

The choice among different approaches is still debated. UNE is contraindicated in patients with previous cervical surgery, large adenomas, genetic and familiar forms of PHPT, lithium treatment, medium-large sized goiter, and parathyroid carcinoma.
BNE, the only approach performed until few years ago, enables cure in over 95% of PHPT, with morbidity lower than 2-3%. Randomized trials comparing BNE to UNE or MIP have been performed, all but one with short follow-up (154). The unilateral approach (either UNE or MIP) performed by a skilled surgeon yields the same cure rate of BNE, with the additional advantage of decreasing post-operative pain and hypocalcemia, as well as shortening surgical time and in-hospital days (155, 156). No trial has compared UNE *vs* MIP.
Since the outcome of MIP-open and MIVAP was largely similar, according to the few randomized studies (157), the choice between these two options is a matter of individual preference of the single surgeon.
As for MIRP, results are controversial. The only randomized study comparing MIRP *vs* BNE showed the same cure rate (158). Retrospective studies on the routine use of MIRP, with or without pre-operative scintigraphic localization, reported excellent results, but without either control group or confirmation in other trials (159-161). MIRP can play a role in selected cases: re-operation or parathyroid ectopy in patients without nodular thyroid disease and with pre-operative positive scintigraphy.
A study in 1158 patients (162) threw shadow on long-term cure after MIP (or UNE). After focused removal of the pre-operatively localized pathological gland, resulting in ioPTH fall consistent with cure, surgeon performed BNE, removing other enlarged hypercellular glands in 16% of patients. These features are regarded as potential source of PHPT relapse, even though others dispute their compulsory pathologic meaning (163).

If a single gland is pre-operatively identified, **we recommend**:
- MIP or UNE if scintigraphy and US are concordant;
- BNE or MIP/UNE with ioPTH if scintigraphy and US are discordant or only one is positive.

If more than one gland is pre-operatively identified or both scintigraphy and US are negative, **we recommend** BNE.
We recommend referral of patients to a skilled surgeon.

As for surgery in genetic and familial PHPT, bearing higher rate of persisting/relapsing disease, no prospective randomized trial has been performed. Surgery must aim to obtain the highest cure rate with the lowest rate of complications, as well as to get easier the re-operation in the case it would be required. BNE is the main indication, involving thymectomy and cryo-preservation of parathyroid tissue. In well-selected cases, such as relapse with positive pre-operative localization, MIP can be applied, and even better MIRP. IoPTH can be usefully employed with cut-offs for cure more restrictive than those used in the sporadic forms (164, 165).

According to the different involvement of parathyroid glands in the different diseases, **we suggest** performing:

- in MEN 1 subtotal PTX or, as second option, total PTX + auto-transplantation;
- in MEN 2A and other non-MEN familial forms (HPT-JT syndrome, FIHPT, autosomal dominant mild PHPT) removal of enlarged glands only.

<u>PHPT and nodular goiter</u>

Nodular thyroid disease is present in up to 70% of PHPT patients, mostly in regions of endemic iodine deficiency. Prevalence of differentiated thyroid carcinoma is higher in these patients (166).

It is advisable to treat nodular thyroid disease concomitantly to PHPT, in order to avoid repetitive surgery that would be more worrisome owing to post-surgical adhesions, in particular after BNE. Even MIP can induce adhesions, mostly after resection of posterior parathyroid glands.

Since MIP does not allow an optimal intra-operative evaluation of thyroid nodules, a pre-operative thyroid US study is warranted.

Only a few retrospective studies were performed about treatment of PHPT in the context of nodular thyroid disease. There are no widely accepted criteria, beyond a broad indication for BNE (165, 167). Guidelines suggest thyroidectomy, mostly if nodular thyroid disease is ipsilateral to parathyroid adenoma (168).

We suggest:

- MIP/UNE when there is indication for hemithyroidectomy that is ipsilateral to pre-operatively localized pathologic parathyroid gland;
- BNE in all the other situations of PHPT and surgical goiter.

Medical management

Some patients with PHPT require medical management because unfitting surgical criteria, failed surgery, comorbidities precluding surgery, or refusal of surgery.

<u>Targeting bone</u>

The combined evaluation of patient's BMD and fracture risk profile may help in selecting patients to be treated. Even though the FRAX algorithm endorsed by World Health Organization to estimate fracture risk has not been validated in PHPT, it is the tool commonly employed in evaluating fracture risk in secondary osteoporosis. The proposed thresholds for pharmacologic treatment (10-yr risk greater than 20% for any fracture or greater than 3% for hip fracture) cannot be applied mechanically to PHPT patients, but FRAX use is encouraged as well.

A number of drugs active on bone have been tested in PHPT. The quality of evidence collected for clodronate (169) and raloxifene (170) is low, and no convincing evidence about the efficacy of these drugs is at present available.

It has been reported that hormone replacement therapy (HRT) increases BMD and decreases fracture risk (171). However, in consideration of the expected long-term duration of bone-targeted therapy in PHPT and taking into account its clinically relevant side effects, HRT does not seem advisable in this setting.

A double-blind, placebo-controlled, cross-over study with alendronate (45) enrolling PHPT patients with T-score <–1.0 at one or more skeletal sites, demonstrated the efficacy of 10-mg/day oral alendronate in decreasing bone turnover and increasing BMD at femoral neck and lumbar spine in a 2-yr period with respect to baseline.

A recent meta-analysis of 40 observational studies and RCT (73) has evaluated the effects of surgical treatment, medical treatment and no treatment on BMD in mild PHPT. The point estimates of the meta-analysis suggest that PTX and anti-resorptive therapy provide similar beneficial skeletal effects in patients with mild PHPT, and that either option is preferable to no treatment.

Successful surgery is usually followed by amelioration of BMD values. Sometimes this does not occur, it occurs slowly, or the bone situation is severely compromised. It seems reasonable to consider alendronate effective, and its administration encouraged, also in these situations.

We recommend considering treatment with alendronate in non-operated patients with PHPT with high-risk profile for fractures.

If the recovery of good bone health status is unsatisfactory after successful PTX, **we suggest** that alendronate treatment should be advised as well.

As a practical tool, alendronate may be started for T-score <–1.5/–2.0 SD and <–2.0/–2.5 SD in PHPT patients with and without additional risk factors for osteoporosis, respectively. Since these BMD thresholds are arbitrarily set, they are to be regarded as merely suggestive. Neither Food and Drug Administration (FDA) nor European Medicine Agency (EMA) have approved alendronate for osteoporosis secondary to PHPT. Thus, the use of alendronate is off-label in this setting.

Vitamin D insufficiency is common in patients with PHPT and may be associated with more severe and progressive disease. There is evidence that vitamin D-deficient patients have increased risk of fractures with respect to vitamin D-replete patients (172, 173). No change in BMD at either the lumbar spine or femoral neck has been demonstrated following

cholecalciferol repletion in these patients, so that the clinical benefits associated with vitamin D repletion in PHPT patients are poor, and no undisputable assumption with regard to bone health can be drawn. However, repletion with cholecalciferol at usual dosages is safe and does not exacerbate hypercalcemia in vitamin D-deficient PHPT patients (14).

We suggest vitamin D supplementation in vitamin D-deficient patients with PHPT, as currently done for non-PHPT patients.

Targeting hypercalcemia

Hypercalcemia must be always specifically addressed when moderate-severe, i.e. serum calcium levels are ≥12 mg/dl. In any case drugs inducing hypercalcemia, such as thiazides, calcium salts, vitamin D or its analogs, as well as digitalis that may produce cardiac arrest, must be stopped. Treatment should start with adequate intravenous hydration followed by furosemide. Intravenous bisphosphonates (clodronate, ibandronate, pamidronate, zoledronate) should be administered until serum calcium levels reduction and patient stabilization. Calcitonin or glucocorticoids may be considered as well. If diuresis is restricted and therapy is ineffective within few hours, in severe cases hemodialysis with a dialysis bath low in or free of calcium is the treatment of choice (98). When patients are stabilized, calcimimetics could be administered to control hypercalcemia. However, expeditious PTX performed by an experienced surgeon remains the definitive cure (98).

Calcimimetics are allosteric modulators of the CaSR located on cells of the parathyroid gland, able to inhibit PTH gene transcription, PTH secretion, and parathyroid cell proliferation. As a consequence, they reduce blood calcium levels. Initially developed for hyperparathyroidism secondary to renal insufficiency, the calcimimetic cinacalcet has been tested in PHPT. In a long-term study (174) cinacalcet 30 mg twice daily orally for up to 5.5 yr maintained normocalcemia with no significant effects on BMD. Marcocci et al (175) have demonstrated the efficacy of cinacalcet in patients with PHPT unresolved after PTX or with contraindication to PTX with a serum calcium concentration greater than 12.5 mg/dl.

Cinacalcet is approved by EMA in "primary HPT for whom PTX would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom PTX is not clinically appropriate or is contraindicated" (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000570/human_med_000903.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125), and by FDA for "treatment of severe hypercalcemia in patients with PHPT who are unable to undergo PTX".

Cinacalcet is well tolerated at low doses but moderate or high doses are often associated to adverse events that may require drug withdrawal.

In severe hypercalcemia **we recommend** adequate hydration and a stepwise approach with furosemide and iv bisphosphonates according to hypercalcemia degree.

We suggest considering cinacalcet treatment (starting with 30 mg/day and escalating along labeling indications according to blood calcium levels and tolerability) in PHPT patients with calcemia more than 1 mg/dl above the upper normal limit and one of the following:

- contraindications to surgery
- unwilling to have surgery
- previously unsuccessful PTX with persisting PHPT
- relapsing PHPT
- long time interval before surgery.

Targeting kidney

Though there are no guidelines or RCT addressing the medical management targeting kidney in PHPT, this should involve regular follow-up to assess renal status and measures to manage kidney stones (21) and preserve renal function. The Italian Society of Nephrology has released recommendations for the management of kidney stones (176) and renal failure (177).

We suggest following the guidelines released by scientific societies of Nephrology for the clinical management of kidney stones and renal failure, keeping in mind that they do not specifically address PHPT patients.

Treatment of PHPT in pregnancy

Surgical cure of PHPT has been reported to decrease the rate of maternal and fetal complications, whereas major complications are reportedly higher with conservative treatment (100).

Pharmacological treatment is the first choice in the 1st trimester. Pregnant women with symptomatic PHPT and serum calcium levels ≥12 mg/dl should receive iv hydration followed by iv furosemide as in-patient, considering calcitonin in women with inadequate fall of serum calcium. Moreover, once PHPT symptoms and hypercalcemia have been medically treated successfully, conservative management with increased oral fluids, decreased calcium intake and/or increased oral phosphate could be performed (99). Anyway, the lack of response when serum calcium level is high and clinical picture is dreadful must prompt surgery, even in an emer-

gency setting. PTX is best performed in the 2nd trimester, whereas in the 3rd trimester PTX is still matter of debate and needs to be evaluated on an individual basis.

We recommend PTX for:
- all women with PHPT during fertile age before planning pregnancy.

We recommend PTX in:
- all pregnant women with symptomatic/severe PHPT.

We suggest that PTX should be offered even to pregnant women with asymptomatic/mild PHPT.
We recommend performing PTX (MIP if possible) during the 2nd trimester.

FOLLOW-UP

Operated on patients

<u>Biochemical follow-up</u>

The early decrease of serum calcium levels to low-normal values in the first hours following surgery heralds cure of PHPT, with vast majority of patients maintaining normal calcium levels in the next weeks/months. Nonetheless successful surgery may occasionally be followed by slow post-operative calcium decrease. Persistent normocalcemia 6 months after surgery depicts curative surgery.
The occurrence of post-surgical hypocalcemia has been minimized by focused, minimally invasive surgical approaches; yet, symptomatic hypocalcemia may be still observed after bilateral PTX and/or in patients with long-standing severe PHPT featuring marked hypercalcemia (155, 178-181).
Long-term surveillance for possible PHPT recurrence is not needed in patients featuring normal biochemical profile at 6 months after surgery for sporadic PHPT (182). However, the possibility of undetected multiglandular and/or familial forms of PHPT should be taken into account.
In patients whose serum calcium levels normalized after PTX, high serum PTH levels (still detected in 9-62%) are not to be regarded as operative failure. This finding is usually transient (fading within a few months), seemingly related to the recovery of bone mineralization (the so called "hungry bone" syndrome). Accordingly, calcium and/or vitamin D supplementation normalizes PTH elevation (183).

<u>Clinical follow-up</u>

Patients surgically cured are typically protected from further bone loss and a marked recovery of BMD may be expected (24, 67, 70, 184). The beneficial effect of surgical cure on BMD may be already apparent after 6-12 months at some sites, while the increase of BMD ranges from 3.8% (femoral neck) to 8.4% (lumbar spine) at 2 yr after PTX (68, 70).
Surgical cure has been followed by a decline of PHPT-associated CV mortality in symptomatic disease (47, 53, 56, 58, 185, 186). Long-term CV monitoring is not routinely required after surgical cure, and should be reserved only to patients with specific risk factors.
A clear-cut reduction of renal complications is observed after PTX (24, 22, 187); yet, surveillance of renal function and/or periodic abdominal US may still be required on individual basis after PTX.
Although some studies suggest that QOL and psychological functioning benefit from PTX (66-68, 70, 188), the clinical utility of monitoring neuropsychological functions in patients operated on for PHPT has not yet been demonstrated.

We recommend close calcium monitoring before early discharge of patients operated on for severe PHPT or after bilateral PTX.
We suggest against long-term surveillance for sporadic PHPT recurrence in patients who are persistently normocalcemic after PTX.
We recommend assessing BMD at 1-2 yr after surgery to establish the effects of PTX.

Non-operated on patients

The management of patients with overt PHPT not amenable to surgical treatment shall encompass the following issues:
- close (e.g. every 3 months) biochemical surveillance;
- BMD monitoring;
- surveillance of CV and neuropsychological functions.

In the last decades, the natural history of untreated mild/asymptomatic PHPT has been addressed by a number of studies. Although the overall number of patients is too limited to draw definite conclusions, the available evidence may be summarized as follows.
- A varying percentage (13.5-37.5%) of untreated patients with mild/asymptomatic PHPT is expected to show some signs of biochemical and/or clinical progression over a 10-15-yr period (24, 187).
- In the short term (1-2 yr) most observational or prospective studies failed to observe a decline of BMD in untreated patients (67, 68). However, a ≥10% of bone loss in the femoral neck and/or the distal radius (i.e. sites rich in cortical bone) has been reported in 29/49 patients not referred to PTX followed-up for 10-15 yr (24).
- Surveillance of patients with mild PHPT is not clearly associated with the development or worsening of neuropsychological and/or CV dysfunc-

tions (53, 67), and survival is apparently unaffected by conservative management (49).

In non-operated patients:
- **we recommend** a long-term follow-up based on yearly biochemical assessment and BMD evaluation every 2 yr;
- **we recommend** the adoption of pharmacological treatment aimed to calcium level control and prevention of fractures (see above) whenever needed.

Genetic and familial forms

Since carrier status can be defined even 20 yr before of clinical manifestations, identification of MEN 1 status helps in clinical management of patients and their relatives. In carriers calcium and PTH levels must be assayed yearly. This monitoring must be life-long because penetrance and severity (i.e. malignancy) of disease cannot be predicted in the individual. This allows lower morbidity at diagnosis and during follow-up, because an early diagnosis of neoplasm (even 10 yr before the clinical manifestations) enables early resection. It is to be underlined, however, that there is no consensus on prophylactic ablation, resulting in controversy about the usefulness of presymptomatic screening.
In MEN 2a calcium and PTH levels are to be assayed yearly in carriers as well as in subjects with familial history of PHPT.
In carriers of mutation of *HRPT2* gene calcium and PTH levels are to be assayed yearly.

We recommend yearly life-long monitoring of calcium and PTH levels in carriers of *MEN 1*, *RET*, and *HRPT2* gene mutations.

CLOSING REMARKS

The Italian Association of Clinical Endocrinologists (AME) is releasing this Position Statement on PHPT in order to help clinicians to manage this disease in an appropriate way. The epidemiological and clinical profile of PHPT has markedly changed. The disease is now very frequent and is the third most common endocrine disorder after diabetes and thyroid disorders. However, the classic form of the disease, with kidney stones, overt bone disease, and marked hypercalcemia, is rare, progressively substituted by mild, asymptomatic, and normocalcemic variants, each with its own diagnostic and therapeutic challenges.
The statement leads the reader through a logical pathway addressing biochemical diagnosis, organ damage (classic and non-classic), procedures for localization of hyperfunctioning gland(s) and finally treatment. It is clearly stated that PTX is still the only curative treatment with high success rate in experienced hands; nevertheless, conservative medical treatment has a recognized and appropriate role in specific situations. Clinicians will find useful the thorough discussion about the surgical indications in borderline situations and the well-defined active role of imaging in clinical decision-making. Finally, a section has been dedicated to addressing PHPT and pregnancy.
We are confident that clinicians will find useful this updated effort that will help them in everyday practice.

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