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Review

Primary hyperparathyroidism and the road to surgery: appraisal of the proceedings of the four international workshops (1990, 2002, 2008, 2014) on primary hyperparathyroidism

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ABSTRACT

Although surgery is unambiguously recommended for symptomatic primary hyperparathyroidism (PHPT) patients, management options for asymptomatic patients have varied between surgery, medications and follow-up. To deal with this issue, four International Workshops have taken place, in 1990, 2002, 2008 and 2014, during which a team of experts drew up criteria to stratify asymptomatic patients as surgery-eligible and surgery-ineligible. The efficacy of the criteria have however been questioned over the years and the majority of patients, both eligible and ineligible, may eventually have undergone surgery. Nevertheless, the criteria are still in use today and they clearly mirror the course of change in the treatment of PHPT patients.

Key words: aPHPT, Asymptomatic, Guidelines, Primary Hyperparathyroidism, PHPT, Treatment, Workshop

INTRODUCTION

Since the emergence of the so-called catch-up effect in the early 1970s when routine serum calcium measurement was introduced and many asymptomatic patients were diagnosed with primary hyperparathyroidism (PHPT) on the basis of a previously occult hypercalcemia, the incidence of PHPT has declined.[1] The majority of patients are now diagnosed by routine laboratory testing at a perceivably asymptomatic stage,[2,3] although only a small percentage of them are truly asymptomatic (approximately 5% in one study).[4] Surgical intervention in the form of bilateral neck exploration (BNE) has been the standard of care for patients with classic hyperparathyroidism (HPT) findings; nevertheless, mild hypercalcemia and lack of symptoms can warrant a nonsurgical monitoring approach, as was first acknowledged in 1990 when the original NIH guidelines on the Diagnosis and Management of Asymptomatic Primary Hyperparathyroidism were issued.[5] Three subsequent Workshops took place in 2002, 2008 and 2014, in which global

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experts in the field reviewed and updated previous concepts, revisiting old claims and incorporating new information.

The therapeutic management of HPT is by no means ambiguous, but there is still room for debate as well as potential for advancement. This review will address the major considerations regarding treatment and follow-up of patients with primary hyperparathyroidism as these have come to light through the Workshops' guidelines over the past few years.

1990: SETTING THE TRENDS

In 1990, following the First International Workshop on PHPT,[5] the specialist panel announced the creation of a new clinical profile of the disease, distinguished by mild hypercalcemia and absence of bone or renal disease, namely, asymptomatic PHPT (aPHPT). They were careful to stress that, even though the condition appeared benign, there was not enough information to support this claim in the long term. They were particularly concerned that chronic exposure to parathyroid hormone (PTH) could lead to silent bone loss and increased fracture risk. Notwithstanding, they did not go as far as to recommend anti-osteoporotic treatment for patients with aPHPT.

In their statement, aPHPT was defined as a biochemically confirmed disease without signs and symptoms attributable to it. "Attributable" is the key word here. Namely, aPHPT patients may well be symptomatic, but neither can said symptoms be easily identified nor can they be attributed to PHPT; the experts referred to "several vague symptoms that cannot be definitively attributed to primary HPT but may instead be nonspecific or arise from a coexisting condition". Subsequently, using questionnaires related to mental health, multiple studies consistently found that parathyroidectomy was followed by Quality of Life improvement in patients who were considered asymptomatic,[6-9] indicating that neuropsychiatric symptoms may be underreported or underestimated and parathyroid surgery can help unmask them.[10]

Although concerned about late complications, the experts agreed that medical monitoring could be considered a viable option for aPHPT patients, when certain criteria were met (serum calcium only mildly elevated/no previous episodes of life-threatening hypercalcemia/normal renal and bone status), but criteria for surgical intervention were also developed (Table I). Moreover, despite the lack of evidence-based specific thresholds, the panel suggested empirical values, upon which general agreement had been

Table I. Guidelines for surgical intervention in aPHPT patients(adapted from original)

Measurement	1990	2002	2008	2014
Serum calcium (> upper limit of normal)	A. 1-1.6 mg/dl B. Life-threatening hypercalcemia	1 mg/dl	1.0 mg/dl	1.0 mg/dl
Renal	A. eGFR reduced by >30% B. 24-h urine for calcium >400 mg/dl C. Presence of kidney stone(s) detected by abdominal radiograph	A. eGFR reduced by >30% B. 24-h urine for calcium >400 mg/dl	A. eGFR <60 ml/min B. 24-h urine for calcium not recommended	A. eGFR <60 ml/min B. 24-h urine for calcium >400 mg/dl and increased stone risk by biochemical stone risk analysis C. Presence of nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or CT
Skeletal	BMD: Z-score <-2.0 (forearm)	BMD: T-score <-2.5 at any site	BMD: T-score <-2.5 at any site and/or previous fracture fragility	A. BMD by DXA: T-score <-2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius B. Vertebral fracture by x-ray, CT, MRI, or VFA
Age	<50y	<50y	<50y	<50y

reached. Serum calcium elevations of 1 to 1.6 mg/dL above the normal range, age-adjusted creatinine clearance reduced by 30% compared to normal, 24-hour urine calcium excretion of more than 400 mg and bone mass with a Z-score of more than two SDs below the mean were all construed as candidacy for surgical treatment. Furthermore, surgical intervention would be considered justified if the patient requested it, consistent follow-up was unlikely, comorbidities complicated medical management or the patient was under 50 years old. The age criterion reflected concern about the long-term outcomes of asymptomatic patients.

Patients who were to be monitored had to appear for follow-up at least twice a year for the next 1 to 3 years, until "the lack of progression had been established". Afterwards, the intervals could be safely lengthened. On each visit, biannually, blood pressure, serum calcium and creatinine measurement with estimation of creatinine clearance were necessary, while annual abdominal radiographs, annual 24-hour urinary calcium in selected patients and bone mass measurement every 1 or 2 years were also recommended. Of course, if in the process the patient developed HPT symptoms or he/she met the criteria for surgical treatment of aPHPT patients, said patient would undergo parathyroidectomy.

The importance of hydration, adequate mobility and a calcium-conscious diet, neither restricted (that could fuel PTH production) nor excessive (that could lead to a hypercalcemic crisis), was stressed, because dehydration, extended immobilization and ill-advised diets could all worsen calcium homeostasis. Moreover, patients were urged to seek medical attention in the event of an illness associated with risk of dehydration (e.g. vomiting, diarrhea).

In regard to parathyroid imaging, preoperative localization was not recommended, since it had not yet been found to be useful, reliable or cost-effective. Besides, it was already evident that imaging had no place in HPT diagnosis.

2002: LOOKING TO ALTERNATIVES

In 2002, the criteria for surgical intervention for aPHPT patients were minimally updated (Table I).[11] The serum calcium threshold was modified to 1 mg/dl above normal range, mirroring concern that patients with higher calcium values might have an increased risk for both symptomatic disease and complications. Furthermore, in regard to bone disease, the criterion of a T-score of more than 2.5 SDs below the mean was substituted for that of a Z-score of more than 2 SDs below the mean, reflecting the notion that BMD in PHPT patients cannot predict fracture risk any more than in populations without PHPT. Therefore, a Z-score, representing deviation from average BMD in a sex- and age-adjusted population and, thus, the effect of the disease itself on bone mass, was considered obsolete, relative to a T-score representing deviation from average peak bone mass.

Although PTH's catabolic effect was thought to primarily target cortical bone (i.e. distal 1/3 radius), some PHPT patients had presented with marked reductions in spinal BMD,[12] whereas significant increases in trabecular bone (i.e. hip) density had been reported after parathyroidectomy.[13] It was therefore suggested that BMD be measured at any of these three sites: distal 1/3 radius, lumbar spine and hip.

Age under 50 years old remained a criterion for operative intervention, this in light of a 10-year observational study that showed approximately a 3-fold increase in likelihood of worsening disease for patients younger than 50 years old.[14]

In regard to neurocognitive and cardiovascular manifestations, which are not traditionally associated with hyperparathyroidism, the experts deemed that their use as criteria for surgery was unsubstantiated.

New monitoring guidelines still comprised biannual serum calcium measurements, annual BMD measurement at any of 3 sites (forearm, lumbar spine, hip) and annual serum creatinine measurement (Table II). But 24h urinary calcium, creatinine clearance (estimated using the Cockcroft-Gault equation) and abdominal X-ray or ultrasound were considered necessary only at initial assessment, not for follow-up.

Medical therapy was hailed as a forthcoming alternative to surgery, yet the experts reaffirmed that parathyroidectomy remained the only definitive means of cure. Estrogens were thought to be useful for postmenopausal women with PHPT, just as they were for postmenopausal women without PHPT,

Table II. Guidelines for the monitoring of aPHPT patients(adapted from original)

Measurement	1990	2002	2008	2014
Serum calcium	Biannually	Biannually	Annually	Annually
24-h urinary calcium	Annually	Not recommended	Not recommended	If renal stones suspected
Creatinine clearance (24-h urine collections)	Annually	Not recommended	Not recommended	Annually
Serum creatinine	Annually	Annually	Annually	Annually
Bone density	Annually (forearm)	Annually (3 sites	Every 1–2 yr (3 sites)	Every 1–2 yr (3 sites)
Abdominal x-ray (± ultrasound)	Annually	Not recommended	Not recommended	If renal stones suspected (±CT)
x-ray or VFA of spine	Not recommended	Not recommended	Not recommended	If clinically indicated (e.g. height loss, back pain)
24-h biochemical stone profile	Not recommended	Not recommended	Not recommended	If renal stones suspected

while raloxifene, bisphosphonates and calcimimetics were considered promising, albeit unsubstantiated options. The significance of adequate calcium intake was emphasized once again, whereas vitamin D supplementation was deemed necessary in patients with vitamin levels below 20 ng/ml.

Most importantly, in 2002, operative alternatives to BNE were officially conceded for the first time. The reason why BNE was the standard of care was that in 15% of cases, PHPT was due to multiglandular disease, so that visualization of all four glands seemed a sensible requirement. Nevertheless, minimally invasive parathyroidectomy (MIP), with preoperative sestamibi scan and intraoperative rapid PTH assays complementing a *unilateral* exploration, was viewed as "one of the most promising techniques". In addition to this, the panel hypothesized that in the future, MIP could well become the procedure of choice provided that long-term patient outcomes were affirmative and surgeons became proficient in the technique.

It is important to note that, traditionally, MIP refers to parathyroidectomy following a *unilateral* neck exploration; nevertheless, there is also a record of a minimally invasive *bilateral* neck exploration which has been advocated by Dr. Norman et al.[15,16] What is more, today most surgeons are able to perform a classic BNE through a small incision of 3.5-5cm that might qualify as "minimally invasive", although it has been proposed that this term be used only in parathyroidectomies with an incision shorter than 2.5 cm.[17] For the purpose of clarity, in this article the term "MIP" should be considered interchangeable with "unilateral neck exploration".

Concerning preoperative localization, with a touch of humor, the panel quoted acclaimed radiologist Dr. John Doppman: "The greatest challenge in preoperative localization of the parathyroid adenoma is locating an experienced surgeon". Indeed, this is one of the few claims that have remained unaltered through the Workshops' consensus statements. Of course, experience is an impactful factor for surgeons and radiologists alike. Sestamibi scanning is the most widely used localizing procedure and its success rate can reach 85% in experienced centers (though only 50-60% in inexperienced ones), at least 5-10% shy of an experienced parathyroid surgeon's own success rate of 90-95%. Preoperative localization was considered necessary only as an adjunct to MIP (in which case, because the exploration is going to be unilateral, the surgeon has to minimize the possibility of a second, contralateral adenoma or diffuse hyperplasia, which would warrant a bilateral exploration) and in the event of previous failed neck surgery.

MAKING WAVES

At this point, a study was conducted to assess whether there was a significant difference, if any at all, in preoperative and postoperative status between

patients who fulfilled the NIH criteria for surgical intervention and those who did not.[18] Both groups, the NIH and the non-NIH, underwent surgery. The group of PHPT patients was also compared to a control group of thyroid patients to evaluate the association of PHPT with 14 nonspecific symptoms, such as fatigue, weakness, back pain, pruritus, etc. Specific PHPT symptoms or conditions could not be used for comparison, since they either justified inclusion in the NIH group (i.e. nephrolithiasis) or pertained to symptomatic PHPT, for which surgery was unambiguously recommended. Indeed, 9 of the 14 symptoms were more common in the hyperparathyroidism group, while there was no difference in their frequency between the NIH and the non-NIH groups. Postoperative improvement in nonspecific symptoms was also equal in both groups. Furthermore, there was no disparity between postoperative outcomes in the two groups; both achieved similar mean serum calcium and PTH values after surgery, while BMD improved significantly. Based on their findings, as well as the conclusion of two 10-year prospective studies that it was impossible to define criteria that could predict disease progression in asymptomatic patients, the researchers questioned the efficacy of the NIH criteria and argued that "virtually all PHPT patients" should undergo surgery by an experienced surgeon.[19,20] Nevertheless, in the aforementioned 10-year prospective study[19] only 25% of asymptomatic patients that did not fulfill the NIH criteria manifested disease progression and required surgery. The majority did well without it.

2008: THE "LONGEST NATURAL HISTORY STUDY" OF PHPT

Once again, data on cardiovascular and neurocognitive manifestations were insufficient to warrant their use in treatment decision-making, but information collected from the Columbia University PHPT Project, a 15-year observational study deemed "the longest natural history study of this disorder", were included in the statement. In that study,[21] subjects that did not have parathyroid surgery were biochemically stable for at least 12 years. PTH, ALP and calcium urinary excretion remained stable for 15 years, but serum calcium levels started rising at year 13. The rise was slight, yet statistically significant. Lumbar spine BMD remained stable throughout the study; however, at year 9, femoral neck and distal 1/3 radius (both sites containing considerable amounts of cortical bone) showed marked reduction in BMD. This reduction led to a 10% decrease in BMD at one or more sites over the 15-year period for 59% of patients, a finding that confirmed the deleterious effect of prolonged bone exposure to PTH excess. Furthermore, the researchers found no significant difference in disease progression rates between those who fulfilled the NIH criteria for surgery and those who did not, inflaming old disputes about the efficacy of the NIH criteria. Finally, 37% of asymptomatic patients who initially did not "qualify" for surgical intervention went on to have surgery. Those findings suggested that non-progression in asymptomatic patients is not unlimited and a nonsurgical approach can be considered safe for only a restricted amount of time and under vigorous monitoring.[22]

In the new guidelines,[23] the criterion of a GFR <60 ml/min was substituted for that of a 30% reduction in creatinine clearance. 24h calcium urinary excretion was dropped from the list owing to evidence that *Ca* urinary excretion varies with age, sex and race, its measurement is not very precise and it is only one of at least six risk factors for kidney stone formation (Table I). Nevertheless, it was pointed out that some physicians still considered a 24h *Ca* urinary excretion of more than 400 mg as an indication for surgery, while it could be useful at initial evaluation, specifically if familial hypocalciuric hypercalcemia was part of the differential diagnosis.

In line with the Official Positions of the International Society for Clinical Densitometry, the panel reviewed the BMD criteria. The new threshold comprised either a T-score of more than 2.5 SDs below the mean for peri- and postmenopausal women and men over 50 years old or a Z-score of more than 2 SDs below the mean for premenopausal women and men under 50 years old.

Regarding patient follow-up, the panel agreed that serum calcium and creatinine should be measured annually, while BMD should be measured every 1 to 2 years at any of 3 sites (forearm, lumbar spine, hip) (Table II), and declines equal to or greater than the least significant change (LSC) should prompt intervention. Evidence that serum creatinine was not

a reliable marker of disease progression were taken into account.

Once again, the need for experienced surgeons was emphasized: "Surgeon experience is considered by virtually all experts to be the single most important variable that has a direct effect upon cure and complication rates for parathyroidectomy". The researchers also quoted a study that suggested a linear correlation between operative volume and outcome in endocrine surgery;[24] in that study, surgeons performing 100 or more endocrine operations per year were associated with better outcome and fewer expenses. In regard to parathyroid surgery, another study found that surgeons performing 50 or more parathyroidectomies per year were associated with better outcome,[25] thus suggesting the rate of 50 operations per year as a threshold for defining parathyroid surgery specialism.

Preoperative localization techniques were also discussed, but this time as part of a routine, with sestamibi scanning being the most common, cervical ultrasound the second most common and invasive techniques, such as FNA, arteriography or venous sampling, reserved for cases when previous neck exploration has failed.

MIP with unilateral neck exploration was recognized as a safe and efficient alternative to BNE.[26] One randomized control study showed that MIP provided the same long-term results as BNE,[27] whereas another tested the hypothesis that MIP would lead to an increased incidence of persistent HPT and refuted that claim.[28]

Ever since, it has been reaffirmed that MIP is superior to BNE in terms of operative time and postoperative pain, with similar recurrence rates.[29] On the contrary, other studies have shown that MIP is followed by a higher recurrence rate, that becomes evident only in the long term (beyond 8 years of follow-up).[30] Similar issues about long-term recurrence rates have been raised by Dr. Norman's team, who advocate for a minimally invasive yet bilateral exploration of the neck, complemented by radioguided estimation of glandular function.[15,16,31] Notwithstanding, it is generally accepted that MIP is superior to BNE, in terms of both cure and complication rate, and should be adopted for the majority of patients with PHPT.[32,33] At this point, it is noteworthy that a 2012 study about the implementation rate of these guidelines showed little convergence between theory and practice; only half of the symptomatic and approximately half of the asymptomatic patients who qualified for surgery actually underwent it.[34] As is usually the case, this could either be the result of miscommunication or an implicit indication that, in practice, stratifying PHPT patients into surgery-eligible and ineligible groups is not efficacious.

Finally, bisphosphonates and hormone-replacement therapy (HRT) were considered as treatment options for PHPT patients for whom "skeletal protection was the primary reason for intervention".[35] Bisphosphonates should be chosen over HRT because of the latter's long-term adverse effects. Raloxifene's effect on BMD has not as yet been studied, whereas cinacalcet has been shown to be effective in lowering serum calcium and PTH levels, but without increasing BMD.

WHAT ABOUT VITAMIN D?

According to the American Endocrine Society's guidelines,[36] vitamin D levels below 30 ng/ml constitute vitamin D insufficiency, while levels below 20 ng/ml constitute vitamin D deficiency. Hypovitaminosis D is highly prevalent even in sunny countries that are not traditionally associated with vitamin D insufficiency; 82% of enrolled adolescents were found to be vitamin D insufficient/deficient in an Italian study,[37] whereas approximately 78% of subjects in a Lebanese study had vitamin D levels below the cut-off of 30 ng/ml, and 44-60% of adult subjects had levels below 20 ng/ml.[38] In fact, it is so prevalent that, as anticipated by the physiological response to vitamin D deficiency, utilization of an unadjusted for vitamin D status PTH normal range is likely to underestimate the true prevalence of hyperparathyroidism. Accordingly, in a study with 280 elderly subjects and a hypovitaminosis D prevalence of 60%,[39] PTH reference ranges were constructed for both the whole sample and the vitamin D sufficient (i.e. serum 25(OH)D concentration >30 ng/ml) proportion of the sample. Approximately 25% of the vitamin D insufficient/deficient subjects had high PTH levels relative to the vitamin D sufficient sample's reference range, reflecting secondary hyperparathyroidism (SHPT). In other words, had the whole sample's normal range been used as a cut-off, SHPT prevalence would have been underestimated

by 25%. Another study showed that using a vitamin D-replete population as reference led to a 20% reduction in the upper PTH reference value, therefore increasing the test's sensitivity.[40]

Issues regarding the PTH reference range were first raised in the 2002 Workshop and have been underlined ever since. In 2008, the panel called for routine measurement of vitamin D levels in patients with PHPT, as well as treatment of deficiency so that vitamin D levels be maintained above 20 ng/ml. Although concerned that vitamin D depletion might exacerbate PTH oversecretion, supplementation could very well lead to worsening of hypercalcemia, which was why, in spite of previous recommendations against it, many doctors choose to restrict calcium and vitamin D supplements. The panel's suggestion was largely based upon a study's results.[41] In that study, vitamin D repletion was associated not only with a 26% reduction in intact PTH and a significant decrease in alkaline phosphatase levels but, interestingly so, also with stable serum calcium and phosphate levels.

What is more, vitamin D insufficiency/deficiency is fairly common in PHPT patients specifically, a probable reason for this being a PTH-mediated increase in 25(OH)D degradation,[42] a hypothesis supported by the reported increase in 25(OH)D after parathyroidectomy.[43,44] Interestingly, a Japanese study found that 1alpha-hydroxylase can be produced within the parathyroid cells and demonstrated that it is 25(OH)D (through intracellular hydroxylation in the parathyroid glands) and not kidney-produced 1,25(OH)D that negatively regulates PTH.[45]

2014: BONES, STONES AND SURGICAL OVERTONES

The new guidelines featured extensive discussion on the subject of BMD measurement techniques, reestablished the prognostic significance of subclinical renal stone disease and endorsed the paradigm shift in operative technique of choice.

As new information about BMD in PHPT patients had been gathered, the panel was forced to revisit old densitometric recommendations.[46] Utilization of high resolution pQCT (HRpQCT) and implementation of the trabecular bone score (TBS) analysis on DXA imaging garnered interest around bone microarchitectural changes (especially those in trabecular bone) that had been neglected up until then. Seeing that a significant number of physicians regularly failed to measure BMD at the 1/3 distal radius site and given that cortical bone DXA data had been found to be more representative of the disease's impact on the skeleton,[47] the panel emphasized the significance of the 1/3 distal radius site BMD measurement in all PHPT patients and noted that when used in adjunction with each other, DXA and TBS yielded results that were more concordant with those of HRpQCT, a method that is highly sensitive, yet impossible to broadly implement.

The panel also stressed the importance of a thorough renal stones profile. They recommended renal imaging (through U/S, X-ray or CT) to detect subclinical stone disease and nephrocalcinosis, and assessment of stone disease risk factors, such as calcium, phosphate and oxalate products in urine, the concentration of urinary inhibitors of stone formation and even testing for genetic polymorphisms. Last but not least, they highlighted the need for "above average fluid intake" in patients that are to be followed without surgery.

Regarding cardiovascular manifestations and neurocognitive dysfunction, once again they concluded that the evidence was insufficient to warrant their routine assessment, let alone their use as criteria for surgery.

On the subject of surgical intervention,[48,49] the criteria for surgery were updated to include the presence of vertebral fractures (to be assessed by X-ray, CT, MRI or VFA), while the 24h urinary *Ca* excretion was reinstated as a criterion, followed by biochemical stone risk analysis and detection of stone disease or nephrocalcinosis by U/S, X-ray or CT (Table I). Similarly, the guidelines for the follow-up of patients ineligible for surgery were updated to match those for surgical intervention: vertebral fracture assessment when clinically indicated and biochemical stone risk analysis and renal imaging when stones are suspected (Table II). Indications for operative intervention during follow-up are listed in a separate table (Table III).

Operative options continued to include both BNE and MIP, but a strong preference towards MIP was underlined. Nevertheless, the panel stressed the importance of surgeons being trained in both techniques, since a significant proportion of patients have multi-

Table III. 2014 Indications for Operative Intervention during Monitoring(adapted from original)

Serum Calcium	>1mg/dl above normal range
Skeletal	T-score <-2.5 SDs below the mean OR BMD reduction > LSC
	Vertebral Fracture
Renal	GFR <60ml/min (Creatinine Clearance)
	Clinical renal stone disease or detection of subclinical disease through renal imaging.

glandular disease and thus can only be treated with BNE.

Medical therapy options for those that did not fulfill the criteria for surgery, those that preferred not to be operated on and those for whom surgery was contra indicated remained largely unaltered.[50] Bisphosphonates and especially alendronate was recommended for increasing BMD, whereas cinacalcet was recommended for lowering serum calcium.

CONCLUSION

Over the years, as the criteria for surgical intervention have evolved, more and more patients have been considered eligible for parathyroid surgery, reflecting the rising body of evidence pointing towards parathyroidectomy as the only means of cure in PHPT patients. Of course, some patients can be successfully followed without surgery, however for a restricted amount of time (approximately 10 years) and under vigorous monitoring. It has become apparent that most PHPT patients will eventually proceed to surgery and, if further evidence attributes non-classical clinical presentations to PHPT, then surgery would be brought forward, since a majority of allegedly asymptomatic patients may actually be symptomatic. Despite some evidence to the contrary, specialists still recommend stratifying the patients to surgery-eligible and ineligible groups, while reinforcing the monitoring process. Operative options may still include bilateral neck exploration and minimally invasive parathyroidectomy following unilateral neck exploration, although nowadays a predilection for MIP seems to be the norm, making surgery easier to accept for both patients and physicians.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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