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Surgical Management of MILD Hyperparathyroidism

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Abstract

Introduction: There is no consensus regarding the management of mild primary hyperparathyroidism (M-pHP). Specific management strategies have been suggested by some authors. We compared the surgical management of patients with M-pHP with that of patients with classic primary hyperparathyroidism (C-pHP) according to The Fourth International Workshop on pHP.

Materials and Methods: Data from 173 patients who underwent parathyroidectomy were reviewed and retrospectively analysed. The management of 32 patients with M-pHPT (18.5%) was compared with that of 141 (81.5%) patients with C-pHPT.

Results: M-pHP patients were more often discovered after being diagnosed with osteoporosis (21.9% vs 7.1%, $p=0.02$), and surgery for chondrocalcinosis was more often carried out (6.3% vs 0%, $p=0.03$) in the M-pHP group. A mini-invasive parathyroidectomy (MIP) was carried out in 81.3% of cases, and 87.5% of patients had a single adenoma. The rate of multiglandular pathology was not different between the groups. The rate of same-day discharge was significantly higher in the M-pHP group (37.5% vs 17.7%, $p=0.01$). Success was achieved in 87.5% of the M-pHP group, with no significant difference from the C-pHP group (92.9%, $p=0.48$). There was no significant difference in imaging performance. Imaging discordance was observed in 18.8% of cases in the M-pHP group and 33.6% of cases in the C-pHP group ($p=0.38$), with no correlation with surgical failure.

Conclusion: This study suggests that by selecting patients on the basis of concordant imaging findings and international recommendations, there is no difference in outcome after the surgical treatment of M-pHP and C-pHP.

Keywords: Mild hyperparathyroidism, normocalcemic, normohormonal, parathyroidectomy

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Abbreviations:

4D-CT: 4D computed tomography
BNE: Bilateral neck exploration
C-pHP: Classic primary hyperparathyroidism
M-pHP: Mild primary hyperparathyroidism
MIP: Minimally invasive parathyroidectomy
NC-pHP: Normocalcaemic primary hyperparathyroidism
NH-pHP: Normohormonal primary hyperparathyroidism
NPV: Negative predictive value
pHP: Primary hyperparathyroidism
PPV: Positive predictive value
PTH: Parathyroid hormone
US: Ultrasound

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Conclusion: This study suggests that by selecting patients on the basis of concordant imaging findings and international recommendations, there is no difference in outcome after the surgical treatment of M-pHP and C-pHP.

1 **Introduction**

2
3 Primary hyperparathyroidism (pHP) is defined by the excessive production of parathyroid
4 hormone (PTH) by one or more abnormal parathyroid glands (adenoma, multiglandular hyperplasia,
5 parathyroid carcinoma) [1]. Its diagnosis is biological and classically associated with hypercalcaemia
6 and an increased PTH level. It is the third most common endocrine disorder [2] and predominates in
7 women over 50 years of age [3]. Currently, the diagnosis is most frequently made in asymptomatic
8 patients due to the systematic performance of biological tests prescribed for another reason [4].

9 New forms of hyperparathyroidism have thus been described, including “mild” primary
10 hyperparathyroidism (M-pHP), with a normal serum calcium level and/or a normal PTH level [5].
11 Despite it being formally recognized at the Third International Workshop on Asymptomatic
12 Hyperparathyroidism in 2008 [6], its management by monitoring or surgery remains a matter of
13 discussion [7–9].

14 The aim of this study was to describe the surgical management of patients with M-pHP in
15 comparison with that of patients with classic HP (C-pHP).

17 **Materials and Methods**

18 This single-centre retrospective study included all patients with primary hyperparathyroidism
19 undergoing a parathyroidectomy between 2000 and 2019 at a university medical centre. Patient records
20 were identified by the Medical Information Department using the following codes: KDQA001, 002,
21 003; KDQC002, 900; KDFA001, 002, 003; KDFC001. Patients with a past history of parathyroid
22 gland surgery and patients with multiple endocrine neoplasia (MEN) were not included. All records
23 with missing histological results and serum calcium values at both the immediate and one-month post-
24 operative time points were excluded. Patients with M-pHP were compared to patients with C-pHP [5,
25 6]. The study was approved by the ethics committee (n° 20.146).

27 1. Definition of mild primary hyperparathyroidism

28 M-pHP includes patients with (i) a normal serum calcium level and an increased PTH level, i.e.,
29 normocalcaemic primary hyperparathyroidism (NC-pHP), and (ii) patients with hypercalcaemia and a
30 normal or non-suppressed PTH level, i.e., normohormonal primary hyperparathyroidism (NH-pHP)
31 [5, 10]. The range for the serum calcium level was 2.2 to 2.6 mmol/L, and the total serum calcium
32 level after correction with serum albumin was used [11]. The standards for PTH were those of the
33 laboratory that performed the assay at the date of the surgical decision, $\pm 10\%$ [12]. We excluded M-
34 pHP patients (i) with secondary hyperparathyroidism, defined as a glomerular filtration rate (GFR)

35 above 60 mL/min, receiving medication (lithium, bisphosphonates, thiazide diuretics,
36 anticonvulsants), with chronic bone disease of a gastrointestinal or hepatic origin, with
37 hypovitaminosis D (selected threshold <30 ng/mL) [5, 12–15] or (ii) with tertiary hyperparathyroidism
38 due to chronic kidney disease [5]. Patients with M-pHP were compared to those with C-pHP. Patients
39 with a vitamin D level below 30 ng/mL were considered to have secondary hyperparathyroidism and
40 were not included in the analysis.

41

42 2. Data collection

43 Baseline data included sex, age at surgery, diagnostic circumstances (nephrological or
44 rheumatological evaluation, clinical signs, incidental discovery for asymptomatic patients [12, 16]),
45 symptoms, osteoporosis (T-score ≤ -2.5 or osteoporotic fracture), osteopenia ($-2.5 < \text{T-score} \leq -1$), pre-
46 operative biology (blood calcium and phosphorus in mmol/L, PTH in pg/mL, vitamin D in ng/mL),
47 treatments and surgical indications. The blood calcium level was measured post-operatively, and the
48 PTH and blood calcium levels were measured at 1 month. The time between surgery and the last
49 examination was collected. All post-operative complications were recorded and were defined as major
50 in the case of the need for secondary surgery, a prolonged hospital stay or a secondary hospitalization
51 and as minor in other cases [17]. Clinical signs were categorized into general signs (pain, cramps,
52 asthenia), neuropsychological signs (memory or concentration disorders, irritability, anxiety,
53 depression), rheumatological signs (symptomatic osteopenia or osteoporosis, chondrocalcinosis, bone
54 pain, polyarthralgia), urological signs (urinary lithiasis), cardiac signs (rhythm disorders, palpitations),
55 and digestive signs (nausea, vomiting, abdominal pain).

56 Radiological data included the type of examination, date, location by quadrant, radiologist's
57 experience and the presence of thyroid nodules on ultrasound. In the case of multiple examinations,
58 only the most recent result was taken into account. Surgical data included the surgical approach (mini-
59 invasive parathyroidectomy (MIP), unilateral or bilateral neck exploration (BNE), sternotomy), type
60 of anaesthesia, and extemporaneous examination when appropriate (considered positive if parathyroid
61 tissue was found pathological or not, negative if other tissue was described). The length of hospital
62 stay was collected. The duration of follow-up was defined as the delay between surgery and the last
63 examination. The final histological result was classified as single or multiple adenoma, uniglandular
64 or multiglandular hyperplasia or non-parathyroid tissue. Surgical success was defined by the
65 normalization of biological markers (serum calcium and/or PTH) at approximately one month post-
66 operatively associated with the removal of a pathological gland [18–20].

67

68 3. Characteristics of diagnostic tests

69 To calculate the sensitivity, specificity, positive predictive value (PPV) and negative predictive
70 value (NPV) of ultrasound and scintigraphy, a gland analysis was performed using the Grimaldi
71 method [19]. The combination of the histological result and biochemical normalization was considered
72 the gold standard. Regardless of the number of glands explored in surgery, it was considered that there
73 were 4 glands per patient (*Table 1*).

74
75 An analysis of the discordance between the ultrasound and scintigraphy results was carried out
76 when the results of both imaging modalities were available [21, 22]. Three groups were defined:
77 concordant, if the number of pathological glands and their location in the quadrant were identical;
78 negative, if neither test identified a pathological gland; and discordant. Discordant cases was classified
79 into 3 subgroups: negative ultrasound/positive scintigraphy (U-/S+); positive ultrasound/negative
80 scintigraphy (U+/S-); and examinations not showing the same location or number of pathological
81 glands (U+/S+).

82 83 4. Statistical analysis

84 Qualitative variables are expressed as numbers and percentages. Quantitative data are expressed
85 as the mean \pm standard deviation (IQR: 25, 75). Comparisons between groups were performed using t-
86 tests for normally distributed variables, the Wilcoxon test for non-normally distributed variables and
87 the chi-squared test or Fisher's exact test for categorical variables. For each analysis, *p* values less than
88 0.05 were considered to be statistically significant. Statistical analyses were performed using JMP Pro
89 Software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

90 91 **Results**

92 A total of 173 patients met the inclusion criteria: 32 (18.5%) in the M-pHP group and 141 (81.5%) in
93 the C-pHP group.

94 1. Descriptive analyses

95 Among the 32 M-pHP patients, 22 had NC-pHP (68.8%), and 10 (31.3%) had NH-pHP.
96 Demographic, clinical, and biochemical data are reported in *Table 2*. The majority of the cases were
97 reported after explorations for osteoporosis or osteopenia (34.4%). Discovery was incidental in 28.1%
98 of cases and after the exploration of general signs in 25% of cases. Patients were symptomatic in 59.4%
99 of cases, with mainly rheumatological signs (40.6%) and general signs (31.3%). Twelve patients had
100 osteoporosis (37.5%), and 2 had osteopenia (6.2%); of them, 8 (57.1%) remained asymptomatic. The
101 main surgical indication was a decrease in bone densitometry (40.6%).

102 No significant differences were observed between the two groups concerning demographic data or
103 symptoms (*Table 2*). The diagnosis of osteoporosis was a circumstance of discovery more frequently
104 in the M-pHP group (21.9% vs 7.1%, $p=0.02$). Surgery for chondrocalcinosis was more often observed
105 in the M-pHP group (6.3% vs 0%, $p=0.03$) and for hypercalcaemia (serum calcium level > 0.25
106 mmol/L of the limit) in the C-pHP group (29.8% vs 6.3%, $p=0.003$). There was no significant
107 difference in the other surgical indications.

108

109 2. Surgical data

110 Data related to surgery and post-operative management are reported in *Table 3*. The average length
111 of stay of M-pHP patients was 2.1 ± 2.2 days (min: 0, max: 7), and twelve patients (37.5%) were
112 discharged on the same day. A minimally invasive parathyroidectomy (MIP) was performed in 81.3%
113 of cases ($n=26$), a unilateral exploration was performed in 6.3% of cases ($n=2$), a bilateral neck
114 exploration (BNE) was performed in 9.4% of cases ($n=3$), and a sternotomy was performed in 3.1%
115 of cases ($n=1$). The final histological result showed a single adenoma in 28 patients (87.5%) and a
116 double adenoma in one patient (3.1%). No uni- or multiglandular hyperplasia was found in the M-pHP
117 group. Normal parathyroid or no parathyroid tissue was found in 3 patients (9.4%).

118 The rate of same-day discharge was significantly higher in the M-pHP group (37.5% vs 17.7%,
119 $p=0.01$). There was no significant difference in anaesthesia, surgery or histology between the M-pHP
120 and C-pHP groups. There was no significant difference regarding post-operative biology between the
121 two groups (*Table 3*).

122 Complications occurred in four patients with M-pHP (12.5%): one patient with severe post-
123 operative hypocalcaemia required intravenous supplementation; one patient presented with
124 hypocalcaemia, which was treated orally; one patient experienced transient inferior laryngeal nerve
125 palsy; and one patient developed a non-compressive haematoma, which was drained under local
126 anaesthesia. There was no significant difference from the C-pHP group, in which 18 complications
127 were reported (12.8%, $p=1.00$).

128

129 3. Radiological data

130 In the M-pHP group, 29 patients underwent both US and scintigraphy, and two patients underwent
131 US only. Localization data were not available for one patient. Data regarding imaging performance
132 are reported in *Table 4*. Twenty patients (62.5%) had concordant US and scintigraphy results, and in
133 these cases, the sensitivity was 100%, the specificity was 98.4%, the PPV was 95%, and the NPV was
134 100%.

135 Six patients (18.9%) had discordant US and scintigraphy results: three, U-/S+; two, U+/S+; and
136 one, U+/S-. In this situation, for US, the sensitivity was 28.6%, the specificity was 94.1%, the PPV
137 was 66.7%, and the NPV was 76.2%. For scintigraphy, the sensitivity was 71.4%, the specificity and
138 PPV were 100%, and the NPV was 76.2%. Among these 6 discordant cases, 3 had 4D computed
139 tomography (4D-CT) data, and for all, the results were concordant with those of scintigraphy, and
140 surgery was based on the scintigraphy/4D-CT results. Overall, 4 had NC-pHP, 2 had NH-pHP, and the
141 surgical indication was based on symptoms or osteoporosis. Surgical failure did not occur in any
142 patient with discordant results. There was no significant difference between the M-pHP and C-pHP
143 groups when the imaging results were discordant: 18.8% had M-pHP, and 33.6% had C-pHP ($p=0.38$);
144 the use of 4D-CT was reported in 6 (50%) cases of M-pHP and 9 cases (23.7%) of C-pHP ($p=0.19$);
145 and complications occurred in one case of M-pHP (16.7%) and 9 cases (23.7%) of C-pHP ($p=1.00$).
146 Finally, surgical failure occurred in no cases of M-pHP and in 5 cases of C-pHP ($p=1.00$).

147 Three M-pHP patients were U-/S-. Among them, two had 4D-CT data. In one case, 4D-CT showed
148 an adenoma, and a surgical cure was achieved; in the other case, the 4D-CT result was not conclusive,
149 and no pathological parathyroid tissue was found during surgery. The third negative patient underwent
150 BNE, which revealed an adenoma, and a cure was achieved. In the C-pHP group, three patients were
151 negative (2.1%, $p=0.08$), and success was achieved in two out of the three.

152 There was no significant difference between the two groups in the performance of US, scintigraphy
153 or 4D-CT (*Table 4*).

154

155 4. Surgical results

156 Success was achieved in 87.5% of cases of M-pHP (28/32). None of the patients presented with
157 recurrence, with an average of 15 months of follow-up (min: 0, max: 149). There was no significant
158 difference in the success rate between the two groups, with a 92.2% success rate in the C-pHP group
159 ($p=0.48$). There were 4 cases of surgical failure, and information regarding the management of these
160 cases is reported in *Table 5*. The rate of a surgical cure was similar in patients with discordant and
161 concordant results, at 88.6% vs 92.2%, respectively ($p=0.48$).

162

163 Discussion

164 M-pHP has been recognized for years [23, 24] and appears to be a separate entity due to its
165 physiopathology and management [25]. However, there are no recommendations for and there is
166 consensus on its management. Some authors, such as Singh Ospina *et al.* [8], advocate for monitoring
167 because they found no significant difference between surgery and monitoring in terms of bone, kidney

168 or heart disease or quality of life. Others advocate for surgery, such as Ambrogini *et al.* [26], who
169 showed improved bone densitometry in M-pHP patients after surgery. In a meta-analysis, Sankaran *et*
170 *al.* [27] showed no superiority for either surgical or medical management and concluded that both are
171 reasonable options, similar to the review by Dawood *et al.* [15]. Hassan-Smith *et al.* [7] explained that
172 there was no obvious consensus regarding the management of these patients and that a
173 multidisciplinary discussion was needed. At our institution, a multidisciplinary committee comprising
174 rheumatologists, endocrinologists, radiologists, biologists and ENT surgeons can discuss treatment
175 (monitoring, medical treatment, surgical treatment) on a case-by-case basis. The Fourth International
176 Workshop recommendations [16] are used to evaluate all of our M-pHP and C-pHP patients for
177 surgical indications. A retrospective analysis of our results showed no difference in the pre-therapeutic
178 assessment or therapeutic choice between the two groups. Additionally, there was no difference in
179 terms of diagnosis, biology, surgery, histology, complications or therapeutic success. The mild nature
180 of hyperparathyroidism did not influence its management. The rates of success and complications were
181 similar in the two groups.

182 The findings in this cohort are comparable with other published data. The number of patients
183 with M-pHP is somewhat low; however, the distribution of NC-pHP and NH-pHP is similar to that
184 reported by Wade *et al.* [28] and Amin *et al.* [29]. The demographic data of our patients are also similar
185 to those in the literature [9, 13, 18, 23]. Rheumatological signs and osteoporosis were more frequent
186 in the M-pHP group. This tendency was found by Traini *et al.* [9] and Koumakis *et al.* [25], who
187 explained it by recruitment bias. Some patients may be referred by rheumatologists who are used to
188 screening for hyperparathyroidism in cases of osteoporosis or chondrocalcinosis. We hypothesized
189 that hyperparathyroidism would be detected earlier in patients with rheumatological diseases
190 undergoing follow-up by specialized rheumatologists in the framework of the assessment of their
191 pathology. Their assessment of M-pHP would then be interpreted as such from the initial management,
192 which might not be the case outside these specialized services. On the other hand, patients with M-
193 pHP have minimal abnormalities in serum calcium and PTH and are referred for management when
194 they have symptoms. However, C-pHP patients may be referred based on biological criteria alone [9,
195 25, 29].

196 The majority of M-pHP patients presented with uniglandular forms, with a prevalence of MIP
197 and single adenoma on histology. Same-day discharge was significantly more frequent in the M-pHP
198 group. This modality, which is highly appreciated by patients[30], reduces the cost of treatment while
199 maintaining safety[31, 32]. Treatment is most frequently performed by the most experienced surgeon
200 on our team to whom patients with M-pHP are referred. This may explain the significant difference,
201 as the surgical management of HPF is relatively new, as is outpatient hospitalization. In addition,

202 contrary to C-pHP patients with a very high serum calcium level or PTH level, the perioperative
203 management of M-pHP patients is made easier due to the exceptional risk of severe hypocalcaemia
204 and “hungry bone syndrome” [33]. The absence of recurrence in the M-pHP group after an average
205 follow-up time of 15 months would suggest that these are true uniglandular forms and not
206 multiglandular forms diagnosed over two stages. Only one patient had a multiglandular form with two
207 adenomas. None of the patients in our study had hyperplasia. In the literature, multiglandular forms
208 with hyperplasia are more frequent in M-pHP patients, occurring at a rate ranging from 13.0% to 36%
209 [9, 10, 18, 25, 28, 34, 35]. Traini *et al.* [9] showed that multiglandular diseases were more often found
210 in patients with NC-pHP (13.0 vs 6.8%, $p<0.05$). Orr *et al.*[18] showed that multiglandular disease
211 was more common in patients with NH-pHP (26.7% vs 14.3%). $p=0.02$). Koumakis *et al.* [25]
212 suggested that the physiopathological origin of NC-pHP may share characteristics with that of
213 secondary hyperparathyroidism by hypothesizing that these patients had a history of long or
214 intermittent hypocalcaemia, which caused the hyperplasia. This difference from the literature can be
215 explained by the fact that in our experience, surgery is mainly proposed for uniglandular forms, while
216 medical treatment is mainly proposed for multiglandular forms. The combined performance of US and
217 scintigraphy examinations and their repetition by experts until agreement is reached increases the
218 diagnostic performance, allows for targeted surgery [21, 36–38] and limits bilateral cervical
219 exploration, which is more likely to cause complications and lead to failure [39].

220 The diagnostic imaging performance in our study is similar to that found by Cheung *et al.*[40]
221 in their meta-analysis of pHP. The diagnostic performance in the M-pHP group is better than in other
222 studies on M-pHP: the sensitivity of US was 76.7%, and that of scintigraphy was 85.7%, versus 52%
223 and 40%, respectively, as reported by Amin *et al.* [29]. Similarly, in a study by Applewhite *et al.* [41],
224 the performance of both US and scintigraphy was significantly lower in the NH-pHP group, and in a
225 study by Orr *et al.* [18], scintigraphy was more often negative in the NH-pHP group (18.3 vs. 4.8%,
226 $p<0.001$). The relatively higher imaging performance in our study is consistent with the higher rate of
227 uniglandular forms [40] The imaging performance correlates well with the success of targeted surgery
228 [42]. Moreover, among 6 patients with discordant imaging results, 4 were successfully managed with
229 targeted surgery, which is similar to the finding reported by De Maissin *et al.* (20). As in the present
230 study, in a former study [21], there were no more NH-pHP patients in the discordant group. Berber *et al.*
231 *al.* [43], in a prospective study of 1000 patients, showed that the pre-operative localization did not
232 depend on the calcium or PTH level but on the BMI and the size and volume of the lesion. Some
233 studies have proven that M-pHP patients have smaller glands than C-pHP patients [29, 35, 41, 44].
234 4D-CT and choline PET have recently increased the rate of identification of pathological glands, but

235 their results are also dependent on the size of the lesion. These modalities are likely to become an
236 important part of the work-up and to increase the success rate of treating M-pHP [45, 46].

237 In our study, the operative cure rate was 91.3%, with no significant difference between the two
238 groups ($p=0.48$). This high operative cure rate is similar to published data. Carneiro-Pla *et al.* [10]
239 found a 95% success rate in a group of M-pHP patients. In NH-pHP patients, the reported rates range
240 from 88% to 98.6% [18, 29, 47], and in NC-pHP patients, they range from 93.8% to 100% [9, 35, 47].
241 In the literature, the definition of a cure is not identical among studies, which makes it difficult to
242 compare success rates. Most studies have chosen normalization of the serum calcium or PTH level at
243 six months, without an associated histological result. We chose to define surgical success by the
244 association of biological normalization and histological excision of a pathological gland, as did
245 Grimaldi *et al.* [19]. Biology alone in NC-pHP patients does not seem to be sufficient to conclude
246 surgical success; in fact, no pathological glands were found in three patients despite post-operative
247 biological normalization. This raises the issue of the biological diagnostic certainty of M-pHP.

248 M-pHP is defined by pHP with a normal serum calcium level and/or a normal PTH level, so
249 quality biological assessment is essential [5]. Biological assays for primary hyperparathyroidism
250 biology have evolved over the last decades. Currently, second- and third-generation assays for PTH
251 should be used [16]. Although we have seen many changes in dosing methods at our institution over
252 the years, the standards taken into account were those of the date of the surgery, and some patients
253 could, in hindsight, be classified in the C-pHP group rather than in the M-pHP group. These patients
254 were nevertheless treated as having M-pHP at the time. This could be a source of bias in the
255 interpretation of the results. Diagnosis can be made with ionized serum calcium, which is more
256 representative of effective calcium stores than the total corrected serum calcium level [23, 24]. The
257 calcium loading test or Pak test could be used to complete this assessment and confirm NC-pHP [48].
258 Finally, hypovitaminosis D can complicate the diagnosis because, in addition to being one of the main
259 causes of secondary hyperparathyroidism [5], it changes the PTH level in primary hyperparathyroidism
260 by 22% [49]. A minimum serum 25-hydroxyvitamin D level of at least 30 ng/mL is recommended by
261 the 2011 report on dietary reference intakes from the Institute of Medicine [50] and by some authors
262 [13, 14, 49]. To avoid this pitfall, only patients with vitamin D normalization were included. Sixteen
263 percent of M-pHP patients initially had hypovitaminosis D, which could be corrected. The biological
264 assessment of M-pHP is therefore more difficult than that of C-pHP and increases the complexity of
265 interpreting the literature because of the significant changes in biological tests and their limit values.

266 **Conclusion**

267 The diagnosis of M-pHP is difficult and requires vitamin D correction and sometimes a calcium
268 loading test. Our results suggest that in M-pHP patients with a normalized vitamin D level, by selecting
269 patients on the basis of concordant imaging findings and international recommendations, the rate of
270 surgical success is as good as that in C-pHP patients. It remains necessary to evaluate the role of new
271 and more specific imaging modalities, such as choline PET, in this particular entity.

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426

Surgical Management of MILD Hyperparathyroidism

Tables

Table 1 : Classification by glands according to the Grimaldi's method.

RESULTS	IMAGING	HISTOLOGY	BIOLOGY
TP	Positive	Pathological or normal	Normalized
TN	Negative	Normal or not explored	Normalized after the removal of another gland
FN	Negative	Pathological	Normalized
FN	Negative	Not explored	Abnormal
FP	Positive	Normal or not explored	Normalized after the removal of another gland

FN = False Negative, FP = False Positive, TN = True Negative, TP = True Positive

Table 2 : Demographic, clinical and biological characteristics of MILD-HP and CHP groups.

	MILD-pHPT	C-pHPT	p value
	n(%) or mn±SD(IQR 25;75)	n(%) or mn±SD (IQR 25;75)	
<i>Patients</i>	32(18.5)	141(81.5)	NA
Age (years) ± SD	61.2±12.5 (52.6 ; 70.8)	58.4±14.7 (51.5 ; 68.3)	p=0.31
Male/Female	5/27(15.6/84.4)	31/110(22/78)	p=0.42
<i>Diagnostic Circumstances</i>			
Incidental Discovery	9 (28.1)	53 (37.6)	p=0.31
General Signs	8 (25)	37 (26.2)	p=0.89
Kidney Stones	4 (12.5)	22 (15.6)	p=0.79
Non-Fractured Osteoporosis	7 (21.9)	10 (7.1)	p=0.02
Fractured Osteoporosis	3 (9.4)	8 (5.7)	p=0.45
Osteopenia	1 (3.1)	1 (0.7)	p=0.34
Neurocognitive Symptoms	0 (0.0)	10 (7.1)	p=0.21
<i>Symptoms</i>			
Asymptomatics	13 (40.6)	55 (39)	p=0.87
Symptomatics	19 (59.4)	86 (61)	p=0.87
Rheumatological Signs	13 (40.6)	42 (29.8)	p=0.23
General Signs	10 (31.3)	40 (28.4)	p=0.75
Urinary Signs	4 (12.5)	26 (18.4)	p=0.42
Cardiovascular Disease	2 (6.3)	2 (1.4)	p=0.16
Abdominal Signs	1 (3.1)	2 (1.4)	p=0.46
Neurocognitive Signs	0 (0.0)	10 (7.1)	p=0.21
<i>Bone Density Decrease</i>			
Osteoporosis or Osteopenia	14 (43.8)	53 (37.6)	p=0.52
Including Asymptomatic	8 (25)	27 (19.1)	p=0.46
<i>Biology</i>			
Serum Calcium (mmol/L)	2.58±0.17 (2.52 ; 2.66)	2.86±0.32 (2.73 ; 2.89)	p<0.01
PTH (pg/mL)	81.86±50.82 (37.0 ; 103.0)	116.36±79.06 (69.5 ; 139.0)	p<0.01
Serum Phosphorus (mmol/L)	0.85±0.31 (0.74 ; 1.0)	0.82±0.26 (0.68 ; 0.97)	p=0.30
Hypophosphoremia	8 (32)	45 (40.9)	p=0.34
Associated Thyroid Disease	8 (25)	35 (24.8)	p=0.98
History of Loboisthmectomy or Thyroidectomy	1 (3.1)	3 (2.1)	p=0.57
<i>Surgical Indication</i>			
Osteoporosis	13 (40.6)	40 (28.4)	p=0.17
Age < 50 years	4 (12.5)	30 (21.3)	p=0.33
Kidney Stones	3 (9.4)	12 (8.5)	p=1.00
Non Specific Symptoms	3 (9.4)	13 (9.2)	p=1.00
Hypercalcemia	2 (6.3)	42 (29.8)	p<0.01
Chondrocalcinosis	2 (6.3)	0 (0.0)	p=0.03
Hypercalciuria	0 (0.0)	1 (0.7)	p=1.00
Others Indications	5 (15.6)	3 (2.1)	p<0.01

SD = Standard Deviation, C-pHPT = Classic Primary Hyperparathyroidism, MILD-pHPT = MILD-Primary Hyperparathyroidism, mn = mean, NA = Not Available

Table 3 : Surgery and Histology characteristics of MILD-HP and CHP groups

	MILD-pHPT n=32	C-pHPT n=141	p-value
	n(%) or mn±SD(IQR 25;75)	n(%) or mn±SD(IQR 25;75)	
<i>Surgery</i>			
Hospitalisation Duration (days) ± SD	2.1 ± 2.2 (0 ; 3)	2.0 ± 1.5 (1 ; 3)	p=0.38
Same Day Discharge	12 (37.5)	25 (17.7)	p=0.01
General Anesthesia	25 (78.1)	126 (89.4)	p=0.14
Hypnosedation	7 (21.9)	15 (10.6)	p=0.14
MIP	26 (81.3)	106 (75.2)	p=0.47
Unilateral Neck Exploration	2 (6.3)	24 (17.0)	p=0.17
BNE	3 (9.4)	11 (7.8)	p=0.73
Sternotomy	1 (3.1)	0 (0)	p=0.18
Frozen-Section Biopsy	22	117	p=0.07
<i>Complications</i>	4 (12.5)	18 (12.8)	p=1.00
Major	1	7	
Minor	3	11	
<i>Histology</i>			
Single adenoma	28 (87.5)	128 (90.8)	p=0.52
Single gland hyperplasia	0 (0.0)	2 (1.4)	p=1.00
Multiple adenomas	1 (3.1)	2 (1.4)	p=0.46
Multigland hyperplasia	0 (0.0)	1 (0.7)	p=1.00
Other histology	3 (9.4)	8 (5.7)	p=0.43
<i>Postoperative</i>			
Postoperative calcium (mmol/L)	2.27 ± 0.13 (2.20 ; 2.34)	2.33 ± 0.18 (2.22 ; 2.42)	p=0.09
One-month calcium (mmol/L)	2.36 ± 0.12 (2.28 ; 2.40)	2.37 ± 0.15 (2.28 ; 2.40)	p=0.70
One-month PTH (pg/mL)	43.40± 25.53 (25.00 ; 54.75)	36.40± 24.40 (19.75 ; 53.00)	p=0.37
Operative cure rate	28 (87.5)	130 (92.2)	p=0.48
During Concordant Imaging (cure/all concordants)	17/20 (85)	68/72 (94.4)	p=0.17
During Discordant Imaging (cure/all discordants)	6/6 (100)	33/38 (86,8)	p=1.00
Surgical failure	4 (12.5)	11 (7.8)	p=0.48

BNE = Bilateral Neck Exploration, C-pHPT = Classic Primary Hyperparathyroidism, MILD-pHPT = MILD-Primary Hyperparathyroidism, MIP = Minimally Invasive Parathyroidectomy, mn = mean, SD = Standard Deviation

Table 4 : Imaging results

	MILD-PH	C-pHPT	p-value
	n=patients/glands	n=patients/glands	
All patients			
<i>Ultrasound</i>	n=124/31	n=124/31	p=0.56
Sensibility	76.7%	76.7%	p=0.94
Specificity	96.8%	96.8%	p=1.00
<i>Scintigraphy</i>	n=116/29	n=116/29	p=0.30
Sensibility	85.7%	85.7%	p=0.22
Specificity	98.9%	98.9%	p=0.32
<i>4D-CT</i>	n=20/5	n=20/5	p=0.19
Sensibility	100%	100%	p=1.00
Specificity	93.6%	93.6%	p=1.00
U/S			p=0.33
concordant	n=80/20	n=80/20	
Sensibility	100%	100%	p=0.34
Specificity	98.4%	98.4%	p=1.00
U/S			
discordant			
<i>Ultrasound</i>	n=24/6	n=24/6	p=0.38
Sensibility	28.6%	28.6%	p=0.45
Specificity	94.1%	94.1%	p=0.58
<i>Scintigraphy</i>	n=24/6	n=24/6	p=0.38
Sensibility	71.4%	71.4%	p=0.23
Specificity	100.0%	100.0%	p=0.60
U/S			p=0.08
negative	n=12/3	n=12/3	

4D-CT = 4 Dimensional Computed Tomography, C-pHPT = Classic Primary Hyperparathyroidism, MILD-HP = MILD-Primary Hyperparathyroidism, U/S = Ultrasound/scintigraphy

Table 5 : Patients with operative failure

MILD Type	Diagnostic Circumstances	Surgical Indication	Imaging	Surgery	Histology	Biology (Ca In Mmol/L, Pth In Pg/ML)	Non-Cure Causes	Evolution
NCpHP T	Osteoporosis	Osteoporosis	U/S concordant	MIP	Adenoma	A 1 month : Ca = 2,75 PTH = 102	Biological	Monitoring
NCpHP T	Arthralgia	Osteoporosis	U/S concordant	Unilateral exploration converts to bilateral	Normal Parathyroid	A 12 months : Ca = 2,30 PTH = 73	Histological	Monitoring
NCpHP T	Osteoporotic fracture	Osteoporosis	U/S negatives 4D-CT : ectopic in laterojugular	Unilateral exploration	Normal Parathyroid	A 23 months : Ca = 2,22 PTH = 106 (standards at 80,1)	Biological and histological	Monitoring
NCpHP T	Incidental	During a cervical surgery	U/S concordant	MIP	Normal Parathyroid	A 2 months : Ca=2,27 PTH = 55,5 (standards at 80,1)	Histological	Monitoring

4D-CT = 4 Dimensional Computed Tomography, NCpHPT = NormoCalcemic Primary Hyperparathyroidism, U/S = Ultrasound/scintigraphy