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Clinical presentation and management of patients with Primary Hyperparathyroidism in Italy

--Manuscript Draft--

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Full Title:	Clinical presentation and management of patients with Primary Hyperparathyroidism in Italy
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Abstract:	Purpose: Evaluation of the phenotype of primary hyperparathyroidism (PHPT), adherence to International Guidelines for parathyroidectomy (PTx), and rate of surgical cure. Method: From January 2014-January 2016, we performed a prospective, multicenter study in patients with newly diagnosed PHPT. Biochemical and instrumental data were collected at baseline and during one-year follow-up. Results: Over the first year we enrolled 604 patients (age 61±14 yrs), mostly women (83%), referred for further evaluation and treatment advice. Five hundred sixty-six patients had sporadic PHPT (93.7%, age 63±13 yrs]), the remaining 38 (6.3%, age 41±17 yrs) had familial PHPT. The majority of patients (59%) were asymptomatic. Surgery was advised in 281 (46.5%). Follow up data were available in 345 patients. Eighty-seven of 158 (55.1%) symptomatic patients underwent PTx. Sixty-five (53.7%) of 121 asymptomatic patients with at least one criterion for surgery underwent PTx and 56 (46.3%) were followed without surgery. Negative parathyroid imaging studies predicted a conservative approach [symptomatic PHPT: OR 18.0 (95% CI 4.2-81.0) p<0.001; asymptomatic PHPT: OR 10.8, (95% CI3.1-37.15) p<0.001). PTx was also performed in 16 of 66 (25.7%) asymptomatic patients without surgical criteria. Young age, serum calcium concentration, 24-h urinary calcium, positive parathyroid imaging (either ultrasound or MIBI scan positive in 75% vs 16.7%, p=0.001) were predictors of parathyroid surgery. Almost all (94%) of patients were cured by PTx. Conclusions: Italian endocrinologists do not follow guidelines for the management of PHPT. Negative parathyroid imaging studies are strong predictors of a non-surgical approach. PTx is successful in almost all patients.
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Author Comments:	Dear Editor, please find attached a revised version of our manuscript, accordingly to your kind suggestions. Manuscript Number: JENI-D-18-00065 Full Title: Clinical presentation and management of patients with Primary Hyperparathyroidism in Italy by Federica Saponaro, Filomena Cetani (both authors contributed equally to the study), Andrea Repaci, Uberto Pagotto, Cristiana Cipriani, Pepe Jessica, Salvatore Minisola, Claudia Cipri, Fabio Vescini, Alfredo Scillitani, Antonio Salcuni, Serena Palmieri, Cristina Eller-Vainicher, Iacopo Chiodini, Bruno Madeo, Elda Kara, Elena Castellano, Giorgio Borretta, Laura Gianotti, Francesco Romanelli, Valentina Camozzi, Antongiulio Faggiano, Sabrina Corbetta, Luisella Cianferotti, Maria Laura De Feo, Andrea Palermo, Giuseppe Vezzoli, Fabio Maino, Marco Scalese and Claudio Marcocci, that we would like to be considered for publication in Journal of Clinical Chemistry and Laboratory Medicine. The present study is the first multicentre Italian study and one of the few European studies that prospectively evaluated the phenotype of Primary Hyperparathyroidism (PHPT), the adherence to guidelines and the rate of surgical cure. It can bring novelty in the field and contribute to improve the clinical management of the disease, that still is the third most important endocrinopaty. The present study has been conducted as part of the research projects of the Mineral and Bone Club of the Italian Society of Endocrinology (SIE). The manuscript has not been submitted to other journals. The manuscript has not been published previously (partly or in full). No data have been fabricated or manipulated (including images) to support your conclusions. No data, text, or theories by others are presented as if they were the author's own ("plagiarism"). The authors declare that they have no conflict of interest. The present manuscrit follows compliance with Ethical Standards: i) Conflict of Interest:

	The authors declare that they have no conflict of interest, ii) Funding: no funding, iii) Human Research: patients signed a specific informed consent, iv) This study has been approved by the appropriate institutional and/or national research ethics committee and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Federica Saponaro, MD, PHD Tel.: +39-3204964028 Email: federica.saponaro@gmail.com Filomena Cetani Tel: +39-050995040 Email: cetani@endoc.med.unipi.it
Response to Reviewers:	Manuscript Number: JENI-D-18-00065 Full Title: Clinical presentation and management of patients with Primary Hyperparathyroidism in Italy We thank the reviewers and the editor for their thoughtful comments that we took into account and made changes in the manuscript accordingly (see tracking in the text). EDITOR I think that, in order to compare the Italian picture with other countries, it might be useful to quote and discuss the following paper recently published in this journal: -Trombetti A et al: Clinical presentation and management of patients with primary hyperparathyroidism of the Swiss Primary Hyperparathyroidism Cohort: a focus on neuro-behavioral and cognitive symptoms. J Endocrinol Invest 2016; 39: 567-576. We kindly thank the editor for this noteworthy suggestion. We changed the text accordingly and compared our results to those of Trombetti et al. along all the Discussion section (see tracking). REVIEWER # 1 In this study the Authors report on the results of a large Italian multicentre prospective study investigating laboratory, clinical and one-year follow-up data in patients with PHPT. The Authors investigate the adherence to the latest guideline of the Fourth International Workshop (2013) for the management of asymptomatic primary hyperparathyroidism. The main conclusions are as follows. 1.Despite the clear suggestions of both the International and Italian guidelines, the adherence to them is weak both in the symptomatic and asymptomatic patients' groups. 2.Despite the lack being among the surgical criteria, the results of imaging studies are strong predictors of choice between surgical versus conservative approach both within the symptomatic and also asymptomatic patients groups. General remarks This is an important and worthwhile study to measure the impact of PHPT guidelines on the therapeutic decisions for PHPT patients regarding conservative vs. surgical approach. Major remarks -Approx. 43% of patients were lost for the one-year follow-up. Patients who were asymptomatic and had negative imaging are probably overrepresented in lost-to-follow-up group. The impact of the high rate of not being followed, as a study bias should be discussed. We thank the reviewer for this comment. Indeed, this group of patients was not lost at follow-up, but were patients of those centers which did not participate to the second part of the study (follow-up). It's not possible to extrapolate the idea that they had a negative imaging rate higher than that of patients reported in the study. The Centers that participated at the second part of the study (18/29 as now clearer in the results section line ≠159) had few patients lost at follow-up. Of note, the lower number of Centers participating the second part of the study is already reported in the limitations (end of discussion). 2. The impact of the results of preoperative imaging investigations (ultrasound and MIBI-scintigraphy) is a very interesting although not unexpected result of the study. Throughout the manuscript, it is not always clear whether the positive/negative results

mean completely negative/completely positive results. What about the discordant results? Were the discordant results considered as negative or positive?
We thank the reviewer and apologize for the inaccuracy. The negative result means concordant negative imaging, i.e. both ultrasound and MIBI scan were negative. Indeed, we did not include the discordant imaging results because we think that we cannot draw conclusions from them. We now have clarified this point along the text and in the Table 3.
3. It would be worthwhile to discuss the (probably unjustified or at least too high) impact of preoperative imaging on the decision making process regarding the choice between conservative vs. surgical treatment.
We completely agree with the reviewer and we added a paragraph (see tracking) in the discussion section, citing International Guidelines and a recent American paper by Wachel et al. on preoperative parathyroid imaging and the decision-making process.
4. Since there are no data about the decision-making process and its main participants, the reviewer is not confirmed that the endocrinologists are the only (mainly?) responsible doctors for this low adherence.
We thank the reviewer for the comment. Indeed, we believe that the endocrinologists are the direct responsible for decision making process in this study, since in all the third level referring centers included in the study, patients were referred and followed-up from specialists. However, also the patient's desire could influence the therapeutic decision, but unfortunately, we have not these data, as already reported in the discussion (line ≠292). We clarify this point at line ≠250-251.
Minor remarks
1.Despite the large number of patients with MEN1, no patients with MEN2. This needs explanation,
We thank the reviewer for this comment. A possible explanation is that MEN2 patients are primarily referred to the oncology service of the Endocrinology Unit, where the preoperative evaluation is made for thyroid and parathyroid therapeutic program.
2.The non-cure rate of 6% seems a bit high. This observation probably reflects the relatively high number of low-volume surgical institutions and would be worthwhile to analyse.
We agree with to reviewer that the non-cure rate of 6% seems too high. However, interestingly, although defined as sporadic PHPT patients, 3 had a multiglandular disease and the histology showed hyperplasia in 2 cases and a double adenoma in one. Therefore, we can hypothesize that these patients might be familial cases with insufficient family history information or "de novo" cases of familial forms of PHPT, as stated in the discussion. Of note, familial PHPT has a higher non cure rate than sporadic PHPT .
4.Typing errors
probably either instead of either line 184 ok
Least instead of last Fig 1 ok

REVIEWER # 2
General Comments:
This is an interesting paper focusing on PHPT clinical management among endocrinologists In Italy. The study demonstrates that a significant number of patients, either with or without symptoms are not managed according to clinical guidelines. Some observations ay help to improve the quality of the paper.

Specific comments:
- Page 5, Material and Methods: It is unclear if laboratory evaluations were made centrally or at the single sites only. If the latter to, how did the authors control for the potential and expected variability in terms of PTH and vitamin D assays particularly?
We thank the reviewer for this important methodological clarification. The laboratory evaluation could not be done centrally, but we checked the relative uniformity of lab tests. Indeed, PTH assays were at least second or third generation and vitamin D assays were mainly CLIA in each center laboratory. We agree that the best would be to centrally perform the measurements, but we encountered many technical and logistic difficulties. We included this point in the study limitations (see discussion).
-There are no data about the type of DXA machines used in the study, nor in terms of cross-calibration or normal data used to define patients as normal or osteoporotic. Please, consider this point carefully.
We understand the point of the reviewer and agree that the centralization of the DXA data would have been the gold standard. However, this was not planned in this study.

	We added this point in the limitation of the study. All the participating centers were third level endocrinology units and used HOLOGIC or LUNAR DXA machines. The definition of osteoporosis was made accordingly to the latest international guidelines for osteoporosis (reference ≠14). We included this clarification in the text in the Materials and Methods and Results sections. - The terms "fragility fractures" and "clinical fractures" need to be better defined. Clinical (symptomatic?) vertebral fractures were then confirmed by X-ray imaging? Which was the method to define a vertebral fracture? We thank the reviewer for this comment. Fragility fractures were defined as and synonymous of symptomatic. We specified this point in the Materials and Methods section. -Table 1 and Table 2: Vitamin D levels were normal in the whole group of patients. Taking into account the very high prevalence of low vitamin D levels in Italy, this observation is rather strange. How can the authors explain the data? We thank the reviewer for this comment. The possible explanation is that the patients were supplemented with vitamin D supplement (by primary medical care), before reaching the endocrinologist. Indeed, the majority of the participating centers recorded the use of vitamin D supplements in the database. - Table 2: vitamin D levels were low in patients with symptoms, irrespective of PTx/no PTx. It seems also that only these patients had this problem (see before). Which is the explanation? Was Low Vitamin D a possible determinant of symptoms? We thank the reviewer for this comment. We agree with the reviewer that low vitamin D could be a determinant of symptoms. Indeed, hypovitaminosis seems to be more prevalent in patients with PHPTthan in geographically matched populations and correlates with severity of the disease (symptoms). Also the increased levels of 1,25-dihydroxyvitamin D in PHPT have also been proposed to influence overall vitamin D status. Possible mechanisms might include an inhibition of the production of vitamin D3 in skin, an inhibition of the production of 25-hydroxyvitamin D in the liver or increased renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D and a shorter half-life of 25-hydroxyvitamin, as discussed in the paper by Silverberg et al. JBMR 2007.
Suggested Reviewers:	Sandro Giannini sandro.giannini@unipd.it His outstanding papers in the field
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Clinical presentation and management of patients with Primary Hyperparathyroidism in Italy

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Concise title: Primary hyperparathyroidism in Italy

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Compliance with Ethical Standards:

- **Conflict of Interest: The authors declare that they have no conflict of interest**

- Funding: no funding

- **Human Research:** This study has been approved by the appropriate institutional and/or national research ethics committee and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

- **Informed Consent:** Informed consent was obtained from all individual participants included in the study.

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This study has been conducted as part of the research projects of the Mineral and Bone Club of the Italian Society of Endocrinology

Abstract

Purpose: Evaluation of the phenotype of primary hyperparathyroidism (PHPT), adherence to International Guidelines for parathyroidectomy (PTx), and rate of surgical cure.

Method: From January 2014-January 2016, we performed a prospective, multicenter study in patients with newly diagnosed PHPT. Biochemical and instrumental data were collected at baseline and during one-year follow-up.

Results: Over the first year we enrolled 604 patients (age 61±14 yrs), mostly women (83%), referred for further evaluation and treatment advice. Five hundred sixty-six patients had sporadic PHPT (93.7%, age 63±13 yrs]), the remaining 38 (6.3%, age 41±17 yrs) had familial PHPT. The majority of patients (59%) were asymptomatic. Surgery was advised in 281 (46.5%). Follow up data were available in 345 patients. Eighty-seven of 158 (55.1%) symptomatic patients underwent PTx. Sixty-five (53.7%) of 121 asymptomatic patients with at least one criterion for surgery underwent PTx and 56 (46.3%) were followed without surgery. Negative parathyroid imaging studies predicted a conservative approach [symptomatic PHPT: OR 18.0 (95% CI 4.2-81.0) p<0.001; asymptomatic PHPT: OR 10.8, (95% CI3.1-37.15) p<0.001). PTx was also performed in 16 of 66 (25.7%) asymptomatic patients without surgical criteria. Young age, serum calcium concentration, 24-h urinary calcium, positive parathyroid imaging (either ultrasound or MIBI scan positive in 75% vs 16.7%, p=0.001) were predictors of parathyroid surgery. Almost all (94%) of patients were cured by PTx.

Conclusions: Italian endocrinologists do not follow guidelines for the management of PHPT. Negative parathyroid imaging studies are strong predictors of a non-surgical approach. PTx is successful in almost all patients.

Key words: parathyroidectomy, parathyroid adenoma, serum calcium, parathyroid imaging.

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disease, characterized by increased serum calcium and high or inappropriately normal serum levels of parathyroid hormone (PTH) [1, 2]. PHPT is prevalent in postmenopausal women and generally due to a single parathyroid adenoma [3]. Clinical presentation of the disease has changed over the last decades in those countries where serum calcium biochemical screening has been introduced. Indeed, in these areas PHPT is commonly diagnosed as an asymptomatic disorder, and a minority of cases are characterized by hypercalcaemic symptoms, nephrolithiasis, bone disease and neuromuscular weakness [4, 5]. Parathyroidectomy (PTx), the only definitive cure for PHPT, should be considered in all patients and recommended in symptomatic patients. The knowledge that even patients with asymptomatic PHPT might experience target organs involvement has led to a long debate about its appropriate management. [6, 7]. The discussion about the need for surgery in asymptomatic PHPT was matter of four Workshops in 1990, 2002, 2008 and 2013 [8, 9], which provided internationally accepted guidelines for PTx in patients with asymptomatic PHPT as well as monitoring for those not undergoing surgery. Some important news and recommendations were introduced in the last International Workshop, particularly regarding the evaluation of bone and kidney involvement and the impact on patient's management [9–13].

Few studies have been focused on the impact of these guidelines on the management of patients with PHPT. In the present study, we prospectively evaluated the phenotype of PHPT in Italy, the adherence to guidelines and the rate of surgical cure.

Materials and methods

Study design

This is a prospective, multicenter study performed in 29 Italian centers for endocrine diseases. Patients with newly diagnosed PHPT in the period January 2014–January 2015 were enrolled and followed for an additional year.

Patients gave their informed consent and the Institutional Review Board of each participating center approved the study.

Patients and data collection

The diagnosis of PHPT was based on elevated ionized or total serum calcium with increased or inappropriately normal intact PTH, according to the normal reference range of each Center.

An *ad hoc* electronic CRF form was developed and used to record all medical data. The CRF was available online, after registration and login at the web site www.hyperparanet.org. The research was open to all endocrinologists in the whole Italian area.

The following clinical data were collected at the baseline visit: age, gender, age at diagnosis, diagnosis of sporadic or familial PHPT, including diagnosis of multiple endocrine neoplasia (MEN) type 1 (MEN1), 2A (MEN2A) and 4 (MEN4), hyperparathyroidism associated-jaw tumor (HPT-JT), familial isolated hyperparathyroidism (FIHP) and familial hypocalciuric hypercalcemia (FHH). Major PHPT features were also recorded, including i) hypercalcemic and neuropsychiatric symptoms ii) symptomatic or asymptomatic nephrolithiasis iii) osteoporosis (T score <-2.5 at any skeletal site by DXA according the latest ~~st~~ International ~~Italian~~ Guidelines for Osteoporosis [14]) iv) previous fragility fractures (defined as symptomatic ~~anamnestic records of symptomatic and/or X-ray documented~~ fractures) v) use of drugs potentially affecting bone metabolism vi) hypertension and major cerebrovascular events. Finally, data about positive or negative imaging studies (neck ultrasound and/or ^{99m}Tc-sestamibi parathyroid scintigraphy), if performed, and information on therapies were also included in the database.

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Biochemical serum and urinary data were collected at baseline and at the last follow-up visit for measurement of: albumin-adjusted serum calcium (Alb-Ca), plasma PTH, 25-hydroxyvitamin D [25(OH)D], creatinine, cholesterol, glucose, triglycerides, 24-h urinary calcium excretion.

After the initial evaluation, the therapeutic planning of each patient with PHPT was selected in the electronic CRF, choosing between two options i) PTx or ii) surveillance with or without medical treatment. A follow-up information on treatment received and histology, where appropriate, were gathered.

Statistical analysis

Results are expressed as means ±SD for continuous variables and median (interquartile range) for non-continuous variables. The Student's t-test, and the Mann-Whitney test were used to compare the continuous and non-parametric variables, respectively. The Chi-square test and Fisher test were used for comparison of categorical variables, as appropriate. A logistic binary regression model was applied to evaluate if age at diagnosis, Alb-Ca, PTH, 24-h urinary calcium, nephrolithiasis, osteoporosis, fragility fractures and concordant positive parathyroid imaging studies were determinants of the choice of PTx. A P value < 0.05 was considered statistically significant. Statistical analysis was carried out using "SPSS Statistics 17.0.1, Chicago, Illinois, USA" and "R, 3.0.2, Auckland, New Zealand".

RESULTS

From January 2014 to January 2015, 29 Italian Centers of Endocrinology, equally distributed in Northern, Central and Southern Italy, participated in the study. Clinical, biochemical and instrumental records of 604 patients with a new diagnosis of PHPT were collected on the web site Hyperparanet. Complete clinical, biochemical, instrumental, histological and one-year follow-up data were available in 345 patients at 18 Centers.

Baseline evaluation of the whole group

The demographic, clinical and biochemical data are summarized in Table 1. The cohort included 604 patients, 502 (83%) females and 102 (17%) males with a female to male ratio of 4.9:1. The mean age was 61±14 years, with a percentage of juvenile cases (age ≤25 years) of 2.8% (n=17). In the latter group, the female to male ratio was significantly lower than in the whole group (1.4:1, P=0.009).

Diagnosis of sporadic PHPT was made in 566 (93.7%) patients and familial PHPT in 38 (6.7%), including 23 cases of MEN1, 6 cases of FIHP, 3 cases of HPT-JT and 6 cases of FHH. *MEN1* gene mutation data were available in 24 cases and mutations were identified in 20.

At least one of the following features was present in 246 (40.7%) patients: i) nephrolithiasis either symptomatic or asymptomatic (i.e., discovered at ultrasound evaluation at the initial workout) (n=177, 29.1%); ii) clinical fragility fractures (n=70, 11.6%); iii) symptoms of hypercalcemia (n=34, 5.6%) as nausea, vomiting and constipation; for the purpose of the present study these patients were classified as "symptomatic PHPT". The remaining 358 (59.3%) patients were asymptomatic. Osteoporosis was detected in 264 (43.7%) of patients and defined accordinggly to the last International ~~Italian~~ Guidelines for Osteoporosis [14]. A history of hypertension or prior major cerebrovascular events was present in 178 (29.5%) and 9 (1.5%) patients, respectively.

After the initial evaluation, PTx was recommended in 281 (46.5%) patients, namely 180 of the 246 (73%) symptomatic and 101of the 358 (28%) asymptomatic patients.

Patients with available follow-up

One-year follow-up data were available in 345 patients from 18 Centers which participated the second part of the study (Fig.1) [289 (83.8%) females and 56 (16.2%) males (F:M=5.2:1), with a mean age of 63±13 years. One hundred fifty-eight (45.8%) patients had nephrolithiasis, clinical fragility fractures and/or symptoms of hypercalcemia and 187

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(54.2%) were asymptomatic PHPT. The majority of patients (n=331, 95.9%) had sporadic PHPT, and the remaining 14 familial PHPT, including MEN1 (n=8), FIHP (n=4), HPT-JT (n=1) and FHH (n=1).

In the whole group, osteoporosis was found in 152 (44.1%) patients and 44 (12.7%) patients complained of neuropsychiatric symptoms (fatigue, depression, agitation, apathy, lack of concentration) upon questioning. A history of hypertension or prior major cerebrovascular events was present in 104 (30.1%) and 5 (1.4%) patients, respectively.

Biochemical data at the baseline visit are reported in Table 1. The characteristics of these patients are similar to those of the entire cohort of 604 patients, with the exception of 24-h urinary calcium and serum 25OHD concentration which were lower, and the rate of nephrolithiasis that was higher (Table 1).

PTx was performed in 87 (55.1%) of 158 patients with symptomatic PHPT, the majority (n=71, 82.6%) of them had nephrolithiasis (Fig.1). Interestingly, despite the general consensus that patients with symptomatic PHPT should undergo surgery, this treatment was not performed in the remaining 71 (44.9%) patients. In order to understand why surgery was not performed, we compared patients who underwent PTx and those who did not. We found that the former (PTx), compared to the latter (no PTx), were younger and had significantly higher mean Alb-Ca, plasma PTH, 24-h urinary calcium and rate of nephrolithiasis, but a lower rate of fragility fractures (Table 2A).

In the remaining 187 patients with asymptomatic PHPT, PTx was advised based on the 2013 guidelines in 121 (64.7%), who met at least one criterion for PTx, but surgery was performed only in 65 (53.7%) of them. Criteria for PTX in the latter group were as follows: serum calcium levels 1 mg above the upper limit of normal range (n=37, 56.9%), osteoporosis (n=35, 53.8%), age <50 yrs (n=14, 21.5%), 24-h urinary calcium >400 mg (n=14, 21.5%). PTx was not performed in the remaining 56 (46.3%) patients, who, compared with patients who did surgery, had a significantly lower rate of serum calcium levels 1 mg above the upper limit of normal range (Table 2B).

PTx group

A total of 279 patients (237 females and 42 males, 158 with symptomatic and 121 with asymptomatic PHPT) had indications for PTx, but surgery was not performed in 127 (45.5%, 71 with symptomatic and 56 with asymptomatic PHPT). The latter patients were older and had a significantly lower mean Alb-Ca, plasma PTH, 24-h urinary calcium and rate of nephrolithiasis, but a higher rate of fragility fractures (Table 2C). It could be hypothesized that in a given patient the decision of not performing surgery was only based upon the above parameters. Interestingly, we found that parathyroid imaging studies were performed in a large proportion of patients [one imaging exam in 251/279 (89.9%) and either ultrasound and MIBI scan in 124/279 (69.3%)] at the initial workout, independently of the therapeutic plan,

i.e. PTx or no PTx. Therefore, the question arises as to whether the results of parathyroid imaging studies might have had a role in the decision-making process. To evaluate this hypothesis a multivariate analysis that included also the results of parathyroid imaging studies was performed in the whole group of patients with indications for surgery. The analysis showed that older age, lower Alb-Ca and, particularly, a higher rate of negative parathyroid imaging studies [concordant negative ~~either~~ ultrasound and ~~or~~ MIBI scan (OR 11.8 95% CI 5.1-27.2, p<0.0001) were independent predictors for the choice of not performing PTx (Table 3). A concordant negative result of parathyroid imaging studies was also a strong predictor of a conservative approach in the subgroups of patients with either symptomatic [OR 18.0 (95% CI 4.2-81.0) p<0.001] or asymptomatic [OR 10.821, (95% CI3.1-37.15) p<0.001)] PHPT (Table 3). We cannot exclude that patient's refusal and comorbidities also accounted for the decision of not undergoing PTx, but unfortunately participants did not report details on this matter.

PTx was also performed in 16 (25.7%) of 66 patients who did not meet the criteria for surgery. These patients, compared with those who did not undergo surgery, were younger (63±8 vs 69±8 p=0.012), had higher Alb-Ca concentration (10.5±0.6 vs 9.9±1.3, P=0.012), 24-h urinary calcium (427±319 vs 201±117, p=0.04), and rate of positive parathyroid imaging (either ultrasound or MIBI in 75% vs 16.7%, P=0.001).

A total of 168 patients underwent PTx, 164/331 with sporadic and 4/14 with familial PHPT. In the former group, the histological diagnosis was a single adenoma in 148 cases (90.3%), double adenoma in 6 (3.7%), atypical adenoma in 2 (1.2%), hyperplasia in 5 (3.0%), and carcinoma in 3 (1.8%). In the familial group, a single adenoma was found in one patient with FIHP, hyperplasia in two with MEN1, and carcinoma in one with HPT-JT.

The large majority (n=158, 94.0%) of patients were cured by PTx. Persistence of PHPT was observed in the remaining 10 patients with apparently sporadic PHPT, in whom the parathyroid histology showed a single adenoma in 7, hyperplasia in 2, and a double adenoma in one.

No-PTx group

The whole group of 177 patients (71 with symptomatic and 106 asymptomatic PHPT) followed without surgery showed a stable clinical and biochemical disease during the one-year follow-up. Indeed, there was no statistically significant difference between baseline and last visit evaluation in Alb-Ca, PTH, 25(OH)D and 24-h urinary calcium (Table 4). Fourteen patients were treated with cinacalcet and 37 with bisphosphonates.

Discussion

This multicenter study was aimed to evaluate the phenotype of newly diagnosed PHPT in Italy, the adherence to the 2013 International Guidelines for the management of asymptomatic PHPT and the rate of surgical cure of PHPT.

PHPT was more frequent in females than males (M/F=4.9:1)), and most common in the 5th-6th decades of life, confirming the finding of a large (n=360) retrospective single-center Italian survey [15]. On the other hand, data retrieved from the "Record of Hospital Discharge" between 2006 and 2011 in 46275 Italian patients under the code "PHPT-related diagnoses and surgical procedures" showed a lower female-male ratio (2.2:1) [16]. It is of note that, under the above code, conditions other than PHPT could have been included, namely "non-tumor-related hypercalcemia", "not-specified hyperparathyroidism" and "other PTx", thus making this cohort not completely comparable with our series. In agreement with our data studies carried out in the USA and Brazil report a female-to-male ratio of 3-4:1 [17, 18].

The clinical presentation of PHPT is highly variable all over the world. In industrialized countries, where automatic biochemical screening is routinely available, the disease is mainly asymptomatic and relevant bone and stone manifestations are unusual. In the present study, the majority of patients (54.2%) were asymptomatic, a percentage that is similar to that (47.8%) reported by Castellano et al. in their retrospective study [15] and by Trombetti et al. (57%) in the prospective Swiss PHPT Cohort Study [19]. In USA, the rate of asymptomatic disease is even higher (80%) [3], while in other countries, like India or China, is very low (around 20%) [20].

In the literature, the terms "mild" and "asymptomatic" are often used as synonymous, but not necessarily the latter patients with asymptomatic PHPT have a mild disease, since they may present moderate hypercalcemia, kidney stones, vertebral fractures accidentally discovered during evaluation, and osteoporosis. To overcome this issue, a recent consensus statement of Italian Society of Endocrinology recommends to define as "mild" patients with asymptomatic PHPT without surgical criteria [21].

Recent studies have shown that, despite the change in the clinical profile of PHPT in Western Countries to a less severe disease, nephrolithiasis remains one of the features of classic PHPT in the modern cohorts. In the present study, we found an overall rate of nephrolithiasis of 29.1%, definitely lower than that (55%) reported in an Italian single-center study [22], but similar to the rate reported in the Swiss population (17%) [19]. The latter study also reported renal stones detected at ultrasound in 35% of patients with asymptomatic PHPT, a figure markedly higher than that (11.3%) reported by Castellano et al. in a retrospective study [23]. Unfortunately, in the present study the electronic CRF was not designed for differentiating silent from symptomatic kidney stones, nor for evaluation the urinary stone risk profile [9].

One of the major aims was to evaluate the adherence of Italian endocrinologists, who were directly involved in the decision-making process in this survey, to the international guidelines for the management of symptomatic and asymptomatic PHPT. Despite the availability of such guidelines since 1991, as well as positions statements of the two major Italian endocrine societies [24] with similar indications, we found that only about half of either symptomatic or asymptomatic patients who met the criteria for PTx underwent surgery. Our data confirm that there is still a suboptimal adherence to the guidelines, both in USA and Europe. Sharata et al., in a retrospective chart-review of 350 primary care clinicians in Oregon, USA, over the period 2009-2011, identified 124 patients with PHPT with no history of prior PTx. PTx was performed in 26/76 (34%) of patients who met criteria for surgery, either because symptomatic or asymptomatic with at least one criterion according to the 2013 guidelines, and in 12/48 (25%) who did not meet surgical criteria. In about half of cases endocrinologists participated in the treatment choice of most primary care physicians. Young age, hypercalciuria and, particularly history of nephrolithiasis were associated with surgery [25]. Yeh et al. identified from the Southern California Kaiser-Permanente Laboratory Management System Patient Database 3388 patients with all the following laboratory values: serum PTH >65 pg/mL, serum calcium >10.5 and serum creatinine >2.5 mg/dl between1995 and 2008. PTx was performed in 134 (50.6%) of 265 patients with symptomatic PHPT (nephrolithiasis) and in 830 (26.6%) of 3123 with asymptomatic PHPT. Of the remaining 3123 with asymptomatic PHPT 569 of 1362 (41.8%) of those who met the Consensus criteria for PTx and 469 of the 1761 (26.6%) who did not were submitted to surgery. Serum calcium >11.5 mg/dL, 24-h urinary calcium excretion ≥ 400 mg and age >50 years were predictive of PTx [26]. Finally~~Also~~, even in the Swiss PHPT population, the guidelines adherence was similar to our results. Indeed, authors evaluated 332 patients, 143 (43%) with symptomatic disease and 189 (57%) with asymptomatic and PTx was performed only in 71/143 (49.6%) symptomatic patients and in 82/131 (62.3%) asymptomatic patients with at least one criterion for PTx [19].

In an attempt to understand why the Italian endocrinologists did not advise PTx in about half of patients who met the current guidelines for surgery, either symptomatic or asymptomatic, we evaluated the role of all variables in the decision-making process. The finding of negative parathyroid imaging studies (concordant negative ultrasound and MIBI scan) strongly predicted the conservative approach. Older age and lower serum calcium concentrations were also independent predictors, but with a lower weight. A relevant role of negative parathyroid imaging studies in not advising PTx in patients with PHPT who met surgical criteria was reported by two recent European studies, both based upon questionnaire-based surveys. Villar del Moral et al. found that 11% of institutions considered PTx contraindicated in patients with asymptomatic PHPT and negative parathyroid imaging studies [27]. A similar attitude was adopted by 15% of Spanish Hospital Endocrinology services [28]. It ~~However, it~~ is noteworthy that international guidelines clearly

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suggest that negative imaging should not inhibit to refer the patient to an experienced parathyroid surgeon, available in Endocrinology third levels centers [13]. Moreover, it was recently demonstrated that preoperative negative imaging is not associated with a decreased surgical cure rate for PHPT ~~primary hyperparathyroidism~~ in a large ~~PHPT~~ population (2185 patients) [29].

As stated by the International Guidelines and the Italian Consensus, PTx should be considered in all patients with asymptomatic PHPT, including those who did not meet the surgical criteria. In this regard it is worth noting that prior randomized clinical trials have shown an improvement in BMD and neuropsychiatric symptoms in those patients who underwent PTx, compared with those who did not PTx [30–32]. Of note in our study, 16 of 66 patients without surgical criteria underwent surgery, and interestingly, the majority of them had positive parathyroid imaging studies, likely accounted for recommending PTx in patients who did not meet the surgical criteria. In the study of Trombetti et a~~l~~l. 11/59 patients without PTx criteria underwent surgery, mainly for the severe neuropsychological complains. Unfortunately, they had no data on parathyroid imaging [19].

PTx was successful in almost all patients (94%) and this is in line with the results of a recent meta-analysis, which included 82 observational and 6 randomized studies and found a final cure rate of 97-98% [33] and with the prospective swiss study (97%) [19].

Persistence of PHPT was observed in 10/168 (6.0%) cases. The persistence of PHPT ranges between 2 and 22% when considering all cases of PHPT [34] and 2.5-5%, when considering sporadic PHPT [35, 36]. Interestingly, all these patients had apparently sporadic PHPT, but 3 had a multiglandular disease at the histology: (2 hyperplasia and 1 double adenoma). Accordingly to other studies, hyperplasia and double adenoma are associated with a significantly higher rate of persistence compared to single adenoma [34]. We cannot exclude that these 3 patients might be familial cases with insufficient family history information or "de novo" cases of familial forms of PHPT.

Fourteen patients had hereditary PHPT, and only 4 of them underwent PTx during the one-year follow-up. This conservative approach in the hereditary forms of PHPT likely depends upon the higher rate of persistence/recurrence compared with sporadic PHPT, unless an extensive surgery, which is associated with a higher risk of complications, is performed. In this regard, Udelsman et al. underline that the surgical approach in hereditary PHPT should aim to achieve normocalcemia for as long as possible, minimizing complications. In this regard the patient's desire and the surgeon's experience, rather that the guidelines for surgery, could influence the therapeutic decision [13]. Interestingly

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all 4 patients undergoing PTx were normocalcemic after surgery, even if the one-year follow is too short to consider them cured.

The strengths of the study are: i) its prospective nature; ii) the inclusion of a large number of Italian Centers equally distributed in the Country; iii) the rather complete clinical, biochemical, instrumental data at baseline, and iv) the one-year follow-up data after PTx or surveillance.

This study has also some limitations: i) 11 out 29 centers did not participate in the one-year follow-up study; ii) all centers were third level referral centers, ~~and~~ iii) the short follow-up, iv) the lack of the intra and inter-assay coefficient of variation between the different centers is also a limit for biochemical analyses and densitometric data.

~~the laboratories measurements were not centrally made. .~~

In conclusion, the present study indicates that Italian endocrinologists working in tertiary referral centers do not follow international guidelines for the management of PHPT. Parathyroid imaging studies are very often performed in the initial patient's workout and negative findings are strong predictors of a non-surgical approach. PTx is successful in almost all patients.

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Legend of Figure

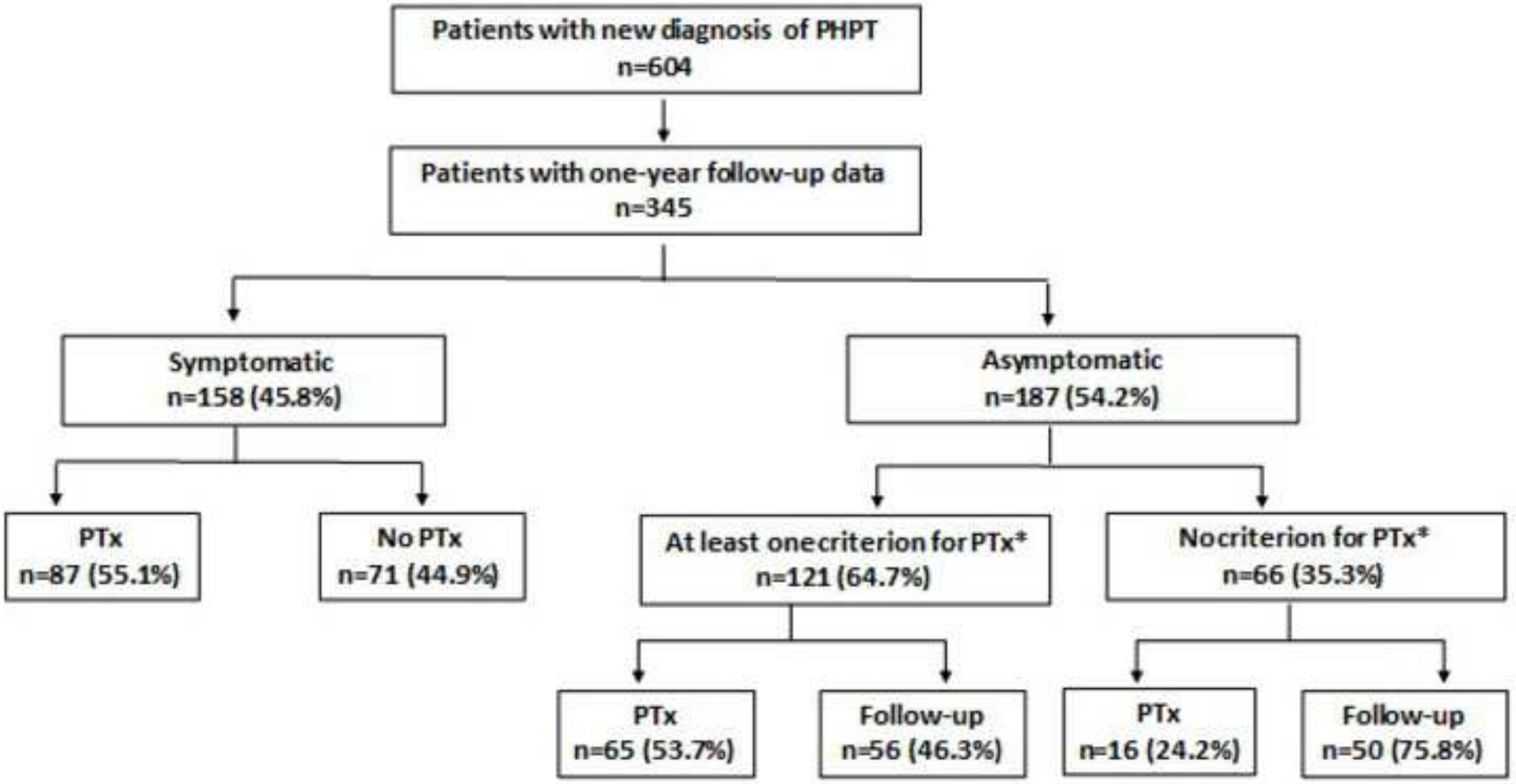
Fig. 1. Flow chart of patients' recruitment, treatment and follow-up.

Abbreviations: PHPT, primary hyperparathyroidism; PTx, parathyroidectomy

- According to the 2013 International Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism

Data Availability: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Figure 1. Flow-Chart of patients recruitment, treatment and follow-up



* According to the 4th International Workshop for Asymptomatic PHPT

Table 1: Clinical and biochemical data of patients in the whole group and in patients with available follow-up

	Whole Group (n=604)	**Patients with available follow-up (n=345)**	***P***
Number of participating Centers	29	18	-
Sex Females n (%) Males n (%)	 502 (83%) 102 (17%)	 289 (83.8%) 56 (16.2%)	0.7
Age at diagnosis (years)	61±14	63±13	0.06
Diagnosis Sporadic n (%) Familial n (%)	 566 (93.7%) 38 (6.7%)	 331 (95.9%) 14 (4.1%)	0.05
Asymptomatic, n (%) Symptomatic, n (%)	358 (59.3%) 246 (40.7%)	187 (54.2%) 158 (45.8%)	0.05
Osteoporosis (T <-2.5 at any site)	264 (43.7%)	152 (44.1%)	0.8
Clinical fractures, n (%)	70 (11.6%)	43 (12.5%)	0.6
Nephrolithiasis, n (%)	177 (29.1%)	119 (34.5%)	0.02
Neuropsychiatric symptoms, n (%)	60 (9.9%)	44 (12.7%)	0.07
Symptoms of hypercalcemia, n (%)	34 (5.6%)	20 (5.8%)	0.5
Albumin-adjusted serum calcium (mg/dL)	10.9±1	10.8±1.3	0.4
Plasma intact PTH (pg/mL)	163±173	152±141	0.2
Serum 25OHD (ng/mL)	30±19	28±14	0.03
Serum creatinine (mg/dl)	0.8±0.2	0.8±0.1	0.3
Urinary calcium excretion (mg/24 h)	326±192	284±186	0.007

Table 2. Comparison between patients who underwent surgery or not in with symptomatic primary hyperparathyroidism (A), in asymptomatic patients with indications to parathyroidectomy (B) and the whole group of patients with indications to parathyroidectomy (C)

A. Patients with symptomatic PHPT[1] (n=158)			
Parameters	**PTx[2] (n=87)**	**No PTx (n=71)**	**P**
Age at diagnosis (years)	56.9±13	65.6±12	0.007
Albumin-adjusted serum calcium (mg/dL)	11.4±1.53	10.4±1.13	<0.001
Plasma PTH (pg/mL)	228.6±225.2	10.5.7±66.8	<0.001
Serum (25OHD) (ng/mL)	14.4±1.8	13.2±1.9	0.001
Serum creatinine (mg/dl)	0.55±0.39	0.63±0.36	0.2
Urinary calcium excretion (mg/24 h)	385.9±200.7	262.7±161	<0.001
Serum calcium >1 mg/dl upper limit of normal	45 (51.7%)	7 (9.8%)	0.0001
Osteoporosis (n%)	36 (41.4%)	33 (46.5%)	0.08
Clinical fractures n (%)	12 (13.7%)	31 (43.6%)	0.001
Nephrolithiasis n (%)	71 (81.6%)	23 (32.4%)	0.033
Hypercalciuria (>400 mg/24h) n (%)	15 (17.2%)	8 (11.3%)	0.02
Neuropsychiatric symptoms n (%)	15 (17.2%)	14 (19.7%)	0.4
Symptoms of hypercalcemia n (%)	13 (14.9%)	7 (9.8%)	0.2
B. Patients with asymptomatic PHPT and surgical criteria[2] (n=121)			
	PTx (n=65)	**No PTx (n=56)**	**P**
Age < 50 years	14 (21.5)	11 (16.9%)	0.4
Serum calcium >1 mg/dL upper limit of normal	37 (56.9)	12 (21.4%)	<0.0001
Hypercalciuria (>400 mg/24h), n (%)	44 (67.7)	30 (53.6%)	0.08
Osteoporosis, n (%)	41 (63.1)	38 (67.8%)	0.5
Serum creatinine (mg/dl)	0.86±0.19	0.82±0.27	0.3
C. Whole group of patients with PTx[3] indications (n=279)			
	PTx (n=152)	**No PTx (n=127)**	**P**
Sex (F:M)	5.7:1	4.7:1	0.3
Age at diagnosis (years)	59.9±13.1	64.7±13.5	<0.001
Albumin-adjusted serum calcium (mg/dL)	11.4±1.3	10.6±1	<0.001

Plasma intact PTH (pg/mL)	190±187	113±77	<0.001
Serum 25(OH)D (ng/mL)	22.2±15.4	26.6±16.7	0.04
Serum creatinine (mg/dl)	0.79±0.17	0.80±0.18	0.7
Urinary calcium excretion (mg/24 h)	257.6±229.7	186.5±168.5	0.015
Serum calcium >1 mg/dl upper limit of normal	82 (53.9%)	19 (14.9%)	<0.001
Osteoporosis (T <-2.5 at any site)	71 (46.7%)	82 (64.5%)	0.05
Clinical fractures n (%)	13 (8.5%)	32 (25.2%)	0.001
Nephrolithiasis n (%)	71 (46.7%)	48 (37.8%)	0.08
Hypercalciuria (>400 mg/24h) n (%)	25 (16.4%)	11 (8.7%)	0.01
Neuropsychiatric symptoms n (%)	15 (9.8%)	14 (11%)	0.4
Symptoms of hypercalcemia n (%)	16 (10.5%)	14 (11%)	0.5

[1] Primary hyperparathyroidism

[2] according to the 2013 International Guidelines for the Management of PHPT

[3] Parathyroidectomy

Table 3. Predictors for the choice of not performing Parathyroidectomy: Results of Logistic Regression Model

Whole group of patients with criteria for Parathyroidectomy[1]			
Parameter	**Odd ratio**	**95% Wald Confidence Limits**	**P value**
Age at diagnosis	1.031	1.007-1.055	0.010
Albumin-adjusted serum calcium	0.515	0.352-0.753	0.001
Concordant negative imaging (ultrasound and~~or~~ MIBI[2] scan~~) negative~~	11.753	5.078-27.205	<0.0001
Asymptomatic patients			
Parameter	**Odd ratio**	**95% Wald Confidence Limits**	**P value**
Albumin-adjusted serum calcium	0.298	0.144-0.619	0.001
Concordant negative imaging (ultrasound and MIBI[2] scan)~~Either ultrasound or MIBI scan negative~~	10.821	3.1-37.15	<0.0001
Symptomatic patients			
Parameter	**Odd ratio**	**95% Wald Confidence Limits**	**P value**
Age at diagnosis	1.048	1.009-1.088	0.016
Albumin-adjusted serum calcium	0.484	0.236-0.991	0.04
Concordant negative imaging (ultrasound and MIBI[2] scan)~~Either ultrasound or MIBI scan negative~~	18.00	4.2-81	<0.0001

[1] according to the 2013 International Guidelines for the Management of PHPT (Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: Summary statement from the fourth international workshop. *J Clin Endocrinol Metab*. 2014;99(10):3561-3569.

[2] ^{99m}Tc-sestamibi parathyroid scintigraphy.

Table 4. Comparison between baseline and one-year follow-up data in patients followed without parathyroidectomy

	Symptomatic patients (n=71)			**Asymptomatic patients (n=106)**					
				Without criteria for PTx[1] (n=50)			**With criteria for PTx (n=56)**		
	Baseline evaluation	**One-year follow-up**	***P*** **[2]**	**Baseline evaluation**	**One-year follow-up**	***P***	**Baseline evaluation**	**One-year follow-up**	***P***
Serum albumin-adjusted calcium (mg/dL)	10.4±1.1	10.9±0.6	0.3	9.6±1.7	10.2±0.6	0.2	10.3±0.7	10.3±0.7	0.7
Plasma intact PTH (pg/mL)	118.3±73	92.6±60.5	0.1	125.9±48.7	123.5±72.3	0.7	115±66	113±61	0.7
Serum 25(OH)D (ng/mL)	30.2±14.1	32.3±9.5	0.02	31.9±12.6	32.8±8.6	0.8	28.4±13	30.9±10	0.1
Serum creatinine (mg/dl)	0.65±0.32	0.82±0.24	0.09	0.65±0.36	0.65±0.33	0.6	0.68±0.35	0.69±0.4	0.5
Urinary calcium excretion (mg/24 h)	235.9±146.9	241.6±156.7	0.5	208.1±104.4	219.4±166.4	0.6	281.9±142.7	275.7±171	0.8

[1] PTx =Parathyroidectomy, according to the 2013 International Guidelines for the Management of PHPT (Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: Summary statement from the fourth international workshop. *J Clin Endocrinol Metab*. 2014;99(10):3561-3569.

[2]one-year vs baseline evaluation

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Full Title: Clinical presentation and management of patients with Primary Hyperparathyroidism in Italy

We thank the reviewers and the editor for their thoughtful comments that we took into account and made changes in the manuscript accordingly (see tracking in the text).

EDITOR

I think that, in order to compare the Italian picture with other countries, it might be useful to quote and discuss the following paper recently published in this journal:
-Trombetti A et al: Clinical presentation and management of patients with primary hyperparathyroidism of the Swiss Primary Hyperparathyroidism Cohort: a focus on neuro-behavioral and cognitive symptoms. J Endocrinol Invest 2016; 39: 567-576.

We kindly thank the editor for this noteworthy suggestion. We changed the text accordingly and compared our results to those of Trombetti et al. along all the Discussion section (see tracking).

REVIEWER # 1

In this study the Authors report on the results of a large Italian multicentre prospective study investigating laboratory, clinical and one-year follow-up data in patients with PHPT. The Authors investigate the adherence to the latest guideline of the Fourth International Workshop (2013) for the management of asymptomatic primary hyperparathyroidism. The main conclusions are as follows.

1. ***Despite the clear suggestions of both the International and Italian guidelines, the adherence to them is weak both in the symptomatic and asymptomatic patients' groups.***
2. ***Despite the lack being among the surgical criteria, the results of imaging studies are strong predictors of choice between surgical versus conservative approach both within the symptomatic and also asymptomatic patients groups.***

General remarks

This is an important and worthwhile study to measure the impact of PHPT guidelines on the therapeutic decisions for PHPT patients regarding conservative vs. surgical approach.

Major remarks

-Approx. 43% of patients were lost for the one-year follow-up. Patients who were asymptomatic and had negative imaging are probably overrepresented in lost-to-follow-up group. The impact of the high rate of not being followed, as a study bias should be discussed.

We thank the reviewer for this comment. Indeed, this group of patients was not lost at follow-up, but were patients of those centers which did not participate to the second part of the study (follow-up). It's not possible to extrapolate the idea that they had a negative imaging rate higher than that of patients reported in the study. The Centers that participated at the second part of the study (18/29 as now clearer in the results section line ≠159) had few patients lost at follow-up. Of note, the lower number of Centers participating the second part of the study is already reported in the limitations (end of discussion).

2. The impact of the results of preoperative imaging investigations (ultrasound and MIBI-scintigraphy) is a very interesting although not unexpected result of the study. Throughout the manuscript, it is not always clear whether the positive/negative results mean completely negative/completely positive results. What about the discordant results? Were the discordant results considered as negative or positive?

We thank the reviewer and apologize for the inaccuracy. The negative result means concordant negative imaging, i.e. both ultrasound and MIBI scan were negative. Indeed, we did not include the discordant imaging results because we think that we cannot draw conclusions from them. We now have clarified this point along the text and in the Table 3.

3. It would be worthwhile to discuss the (probably unjustified or at least too high) impact of preoperative imaging on the decision making process regarding the choice between conservative vs. surgical treatment.

We completely agree with the reviewer and we added a paragraph (see tracking) in the discussion section, citing International Guidelines and a recent American paper by Wachel et al. on preoperative parathyroid imaging and the decision-making process.

4. Since there are no data about the decision-making process and its main participants, the reviewer is not confirmed that the endocrinologists are the only (mainly?) responsible doctors for this low adherence.

We thank the reviewer for the comment. Indeed, we believe that the endocrinologists are the direct responsible for decision making process in this study, since in all the third level referring centers included in the study, patients were referred and followed-up from specialists. However, also the patient's desire could influence the therapeutic decision, but unfortunately, we have not these data, as already reported in the discussion (line ≠292). We clarify this point at line ≠250-251.

Minor remarks

1. ***Despite the large number of patients with MEN1, no patients with MEN2. This needs explanation,***

We thank the reviewer for this comment. A possible explanation is that MEN2 patients are primarily referred to the oncology service of the Endocrinology Unit, where the preoperative evaluation is made for thyroid and parathyroid therapeutic program.

2. ***The non-cure rate of 6% seems a bit high. This observation probably reflects the relatively high number of low-volume surgical institutions and would be worthwhile to analyse.***

We agree with to reviewer that the non-cure rate of 6% seems too high. However, interestingly, although defined as sporadic PHPT patients, 3 had a multiglandular disease and the histology showed hyperplasia in 2 cases and a double adenoma in one. Therefore, we can hypothesize that these patients might be familial cases with insufficient family history information or "de novo" cases of familial forms of PHPT, as stated in the discussion. Of note, familial PHPT has a higher non cure rate than sporadic PHPT .

4. ***Typing errors***
   probably either instead of either line 184 ok
   Least instead of last Fig 1 ok

REVIEWER # 2

General Comments:
This is an interesting paper focusing on PHPT clinical management among endocrinologists In Italy. The study demonstrates that a significant number of patients, either with or without symptoms are not managed according to clinical guidelines. Some observations ay help to improve the quality of the paper.

Specific comments:
- Page 5, Material and Methods: It is unclear if laboratory evaluations were made centrally or at the single sites only. If the latter to, how did the authors control for the potential and expected variability in terms of PTH and vitamin D assays particularly?

We thank the reviewer for this important methodological clarification. The laboratory evaluation could not be done centrally, but we checked the relative uniformity of lab tests. Indeed, PTH assays were at least second or third generation and vitamin D assays were mainly CLIA in each center laboratory. We agree that the best would be to centrally perform the measurements, but we encountered many technical and logistic difficulties. We included this point in the study limitations (see discussion).

-There are no data about the type of DXA machines used in the study, nor in terms of cross-calibration or normal data used to define patients as normal or osteoporotic. Please, consider this point carefully.

We understand the point of the reviewer and agree that the centralization of the DXA data would have been the gold standard. However, this was not planned in this study. We added this point in the limitation of the study. All the participating centers were third level endocrinology units and used HOLOGIC or LUNAR DXA machines.

The definition of osteoporosis was made accordingly to the latest international guidelines for osteoporosis (reference ≠14). We included this clarification in the text in the Materials and Methods and Results sections.

- The terms "fragility fractures" and "clinical fractures" need to be better defined. Clinical (symptomatic?) vertebral fractures were then confirmed by X-ray imaging? Which was the method to define a vertebral fracture?

We thank the reviewer for this comment. Fragility fractures were defined as and synonymous of symptomatic. We specified this point in the Materials and Methods section.

-Table 1 and Table 2: Vitamin D levels were normal in the whole group of patients. Taking into account the very high prevalence of low vitamin D levels in Italy, this observation is rather strange. How can the authors explain the data?

We thank the reviewer for this comment. The possible explanation is that the patients were supplemented with vitamin D supplement (by primary medical care), before reaching the endocrinologist. Indeed, the majority of the participating centers recorded the use of vitamin D supplements in the database.

- Table 2: vitamin D levels were low in patients with symptoms, irrespective of PTx/no PTx. It seems also that only these patients had this problem (see before). Which is the explanation? Was Low Vitamin D a possible determinant of symptoms?

We thank the reviewer for this comment. We agree with the reviewer that low vitamin D could be a determinant of symptoms. Indeed, hypovitaminosis seems to be more prevalent in patients with PHPTthan in geographically matched populations and correlates with severity of the disease (symptoms). Also the increased levels of 1,25-dihydroxyvitamin D in PHPT have also been proposed to influence overall vitamin D status. Possible mechanisms might include an inhibition of the production of vitamin D3 in skin, an inhibition of the production of 25-hydroxyvitamin D in the liver or increased renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D and a shorter half-life of 25-hydroxyvitamin, as discussed in the paper by Silverberg et al. JBMR 2007.