

Preoperative imaging evaluation in primary hyperparathyroidism and associated thyroid disease



Ann. Ital. Chir., 2021 92, 5: 471-478
pii: S0003469X2103044X

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BACKGROUND: Primary hyperparathyroidism (pHPT) is an endocrinological disorder characterized by excessive secretion of parathormone. Minimally invasive approach has become a widespread surgical method for pHPT treatment due to the improvement of preoperative gland localization imaging techniques and the use of intraoperative PTH dosage (IOPTH). We discuss the results of different imaging technique.

MATERIALS AND METHODS: We have conducted a retrospective analysis of 80 patients that underwent surgery for primary hyperparathyroidism in the period between 01/01/2012 and 28/02/2018 and we have focused our data collection on preoperative study, intraoperative findings and follow-up data. We have evaluated the concordance between the findings of the most used imaging techniques, copresence of thyroid disease and IOPTH.

RESULTS: SPECT-CT showed the best results in terms of positivity (93.1%), sensitivity (88.9%) and accuracy (82.8%). Neck ultrasound resulted to have the best positive predictive value (94.4%). IOPTH decrease was correlated with patients' healing ($p < 0.05$). Age lower than 70 years, post-operative calcium and PTH serum levels were related to a higher chance of healing ($p < 0.05$).

CONCLUSION: US-scintigraphy combination is suitable for preoperative evaluation and SPECT/CT confirms to be the best additional examination; the presence of thyroid disease decrease the sensitivity. IOPTH is an important predictor of healing

KEY WORDS: Intraoperative PTH, Hyperparathyroidism, Parathyroidectomy, SPECT/CT, Thyroid disease

Introduction

Primary hyperparathyroidism (pHPT) is an endocrinological disorder characterized by excessive secretion of parathormone by one or more parathyroid glands, resulting in hypercalcemia and hypophosphatemia.

Considering affected patients, 80% present a single adenoma while a minority of cases is caused by gland hyperplasia (12%-25%) and carcinoma (<1%)¹.

In Western countries, blood calcium test and screening for osteoporosis have led to an increased incidence of pHPT diagnosis, also in asymptomatic patients^{4,5}.

Surgery is the only definitive treatment for pHPT and is recommended also for asymptomatic patients, with a cure rate over 95%⁴⁻⁷. In the last two decades, minimally invasive parathyroidectomy (MIP) has become a widespread approach for single adenoma. MIP has the same cure rate and less complications than Bilateral Neck Exploration (BNE) but requires accurate preoperative localization with imaging techniques and use of intraoperative parathyroid hormone (IOPTH)^{6,8-10}.

Both neck ultrasound and dual phase scintigraphy with ^{99m}Tc-MIBI are commonly used for preoperative evaluation in patient undergoing surgical procedures for pHPT^{6,8,11-14}.

SPECT/CT has been recently introduced as additional imaging method to the combined approach of sono-

Pervenuto in Redazione Gennaio 2019. Accettato per la pubblicazione Luglio 2019.

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graphy and scintigraphy^{8,15}. SPECT/CT provides three-dimensional (3-D) topographic information fused with functional ones, thus further improving the detection ability and precise localization of the diseased gland and subsequent surgical planning¹⁶⁻¹⁸.

CT and MRI are more selectively used for cases of multiple glands hyperplasia, ectopic adenoma, negative results from sonography and scintigraphy or recurrent/persistent pHPT^{6,8,15,19}.

IOPTH dosage is an intraoperative test firstly recommended for MIP, but recent studies suggest using it only in case of discordant preoperative imaging^{6,10,20,21}.

The aim of our study was to evaluate the results of preoperative imaging technique and to analyze the impact of IOPTH on surgical outcome.

Materials and Methods

In this retrospective study we have examined all the cases of primary hyperparathyroidism that underwent surgery in the Unit of General Surgery of the University Hospital of Parma, Italy, in the period between January 2012 and February 2018.

In the observed period, 92 patients underwent parathyroidectomy for pHPT, but only 80 were included in our study. We have excluded: 5 patients with diffuse hyperplasia, 3 patients with recurrent / persistent pHPT after surgery (2 of whom had MEN1), 3 cases of ectopic adenomas in the mediastinum, 1 case of intrathyroidal adenoma.

Surgical treatment has been proposed to symptomatic and asymptomatic patients, according to the most recent guidelines²²⁻²⁷. Surgical procedure was chosen on the basis of the results of preoperative imaging: patients with

single adenoma and positive and concordant imaging studies were considered suitable for a minimally invasive procedure, in particular Minimally invasive videoassisted parathyroidectomy (MIVAP)²⁸; patients with negative and discordant imaging studies were candidates for bilateral cervical exploration. Minimally invasive procedure was converted to bilateral cervical exploration in the following cases: failure to identify the adenoma or presence of two or more adenomas.

We have analyzed data collected in a database after authorization by institutional ethics committee, including: age, sex, coexisting thyroidal pathology, serum calcium and PTH levels, type of surgical procedure, IOPTH values, follow-up and imaging techniques used for preoperative evaluation (sonography, scintigraphy, SPECT/CT, CT, MRI) (Figs. 1, 2, 3).

Sonography was performed by an endocrinologist or radiologist.

Follow-up consisted in serum calcium and PTH levels dosage six months after surgery: healing was defined as the persistence of normal calcium levels (<10.4 mg/dL) for at least 6 months after surgery, according to the most recent guidelines of the American Association of Endocrine Surgeons.

We have considered PTH and IOPTH serum levels of 12-88 pg / mL as normal values.

We have correlated IOPTH serum levels and follow-up PTH serum level (available for 59 patients) to the concordance or discrepancy of imaging techniques used for preoperative evaluation.

We have also sought a possible significant difference in mean calcium and PTH serum levels between patients with persistent high IOPTH levels and in those with at least a 50% decrease.

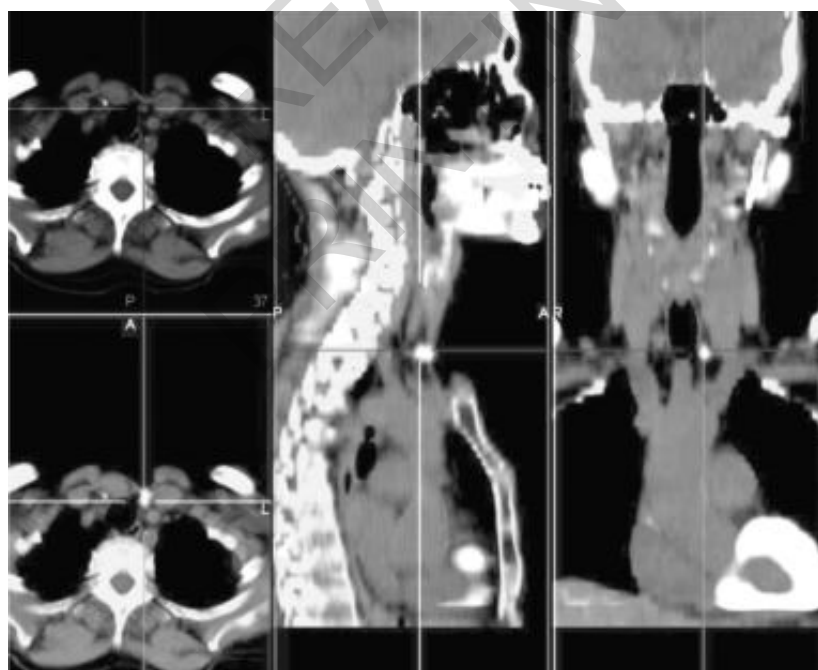


Fig. 1: 99 mTC-MIBI, SPECT CT: Left inferior parathyroid adenoma.

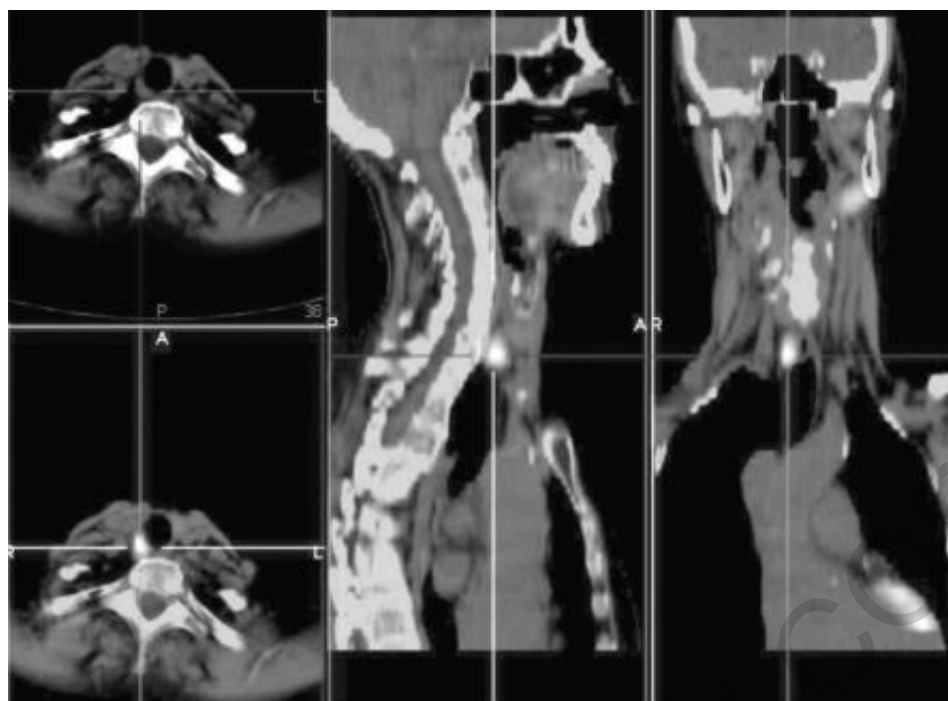


Fig. 2: ^{99m}Tc -MIBI, SPECT CT: right inferior parathyroid adenoma.

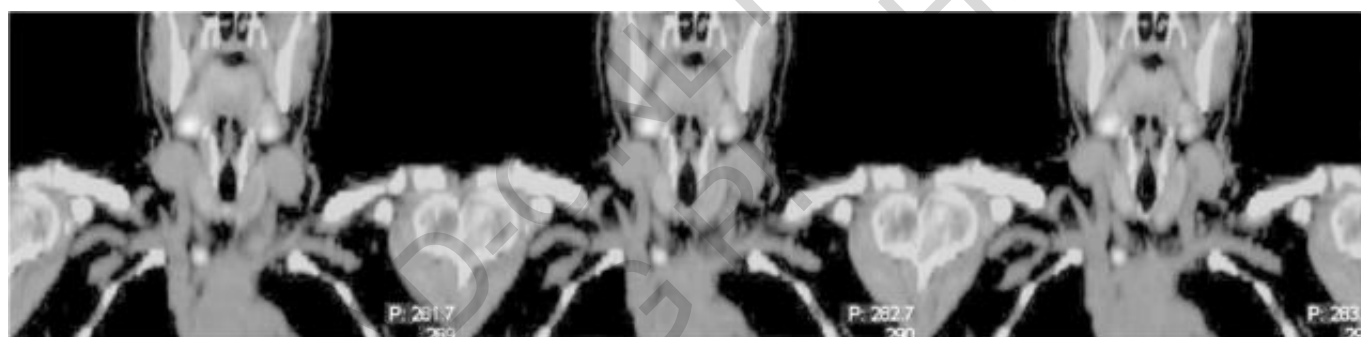


Fig. 3: Ectopic gland.

PREOPERATIVE IMAGING EVALUATION

To evaluate the ability of an imaging technique to detect an adenoma, we have adopted the following definitions:

- true positive result (TP): imaging technique location of the adenoma (right / left or upper / lower) corresponds to the intraoperative finding;
- false positive result (FP): imaging technique location of the adenoma (right / left or upper / lower) does not correspond to the intraoperative finding;
- false negative result (FN): any negative result of the imaging technique;
- true negative result (TN): does not exist because all patients involved in the study are affected by pHPT.

Based on these parameters, we have calculated sensitivity, positive predictive value (PPV) and accuracy for each imaging technique and for each location (right /

left and upper / lower), according to the following formulas:

- Sensitivity = $\text{TP} / \text{TP} + \text{FN}$;
- Positive predictive value (PPV) = $\text{TP} / \text{TP} + \text{FP}$;
- Accuracy = $\text{TP} / \text{TP} + \text{FP} + \text{FN}$.

Specificity and negative predictive value (NPV) could not be calculated due to the absence of true negative results.

We have also analyzed positivity rate for each imaging technique, which corresponds to the percentage of cases in which we had an imaging finding, regardless of the correctness of the adenoma location.

Sensitivity (right-left) and positivity of sonography and scintigraphy were calculated separately in patients affected or not by thyroid disease of surgical interest.

We have evaluated the concordance of the most frequently used techniques in preoperative evaluation: neck ultrasound, dual phase scintigraphy, SPECT/CT.

Follow-up data, available for 59 patients, allowed us to calculate the cure rate. We have divided these 59 patients in different sub-categories: age over 65, age under 65, female, male, positive US, positive scintigraphy, positive SPECT/CT.

We have considered also pre- and post-operative PTH and calcium serum level and the different surgical procedures.

STATISTICAL ANALYSIS

Statistical data analysis was performed using SPSS (version 20.0; SPSS Inc. Chicago, IL, USA). We have used Fisher's Exact Test to compare parametric variables and Student's T test to compare non-parametric variables. Cohen's Kappa coefficient was used to evaluate the concordance between two different imaging techniques. P value <0.05 was considered statistically significant.

Results

This study included 80 patients with preoperative diagnosis of pHPT that underwent surgical treatment between January 2012 and February 2018, 64 (80%) females and 16 (20%) males. The average age was 57 ± 3 years. A concomitant thyroid disease of surgical interest was present in 19 patients (23.75%). Mean preoperative calcium and PTH serum levels were respectively 11.1 ± 1 mg / dL and 286 ± 65 pg / mL. (Table I)

TABLE I - Demographic and preoperative data.

Variables	
Male	16 (20%)
Female	64 (80%)
Age	57 ± 3 (24 – 80)
Preoperative calcium serum levels (mg/dL)	11.1 ± 1 (8,9 -16,5)
Preoperative PTH serum levels (pg/mL)	286 ± 65 (93 – 2391)
Thyroid disease	19 (23,75%).

TABLE II - Imaging techniques used in the preoperative evaluation.

	Neck Us	Dual phase scintigraphy	Spect/Ct	Mri*	Ct*
Positivityrate	78,4%	82,6%	93,1%	100%	100%
Sensitivity (Right/Left)	72,9%	76,6%	88,9%	83,3%	100%
Sensitivity (Inferior/Superior)	63,9%	68,7%	79,3%	83,3%	66,7%
Ppv(Right/Left)	94,4%	90,7%	92,3%	100%	100%
Ppv (Inferior/Superior)	95,8%	97,9%	100 %	100%	100%
Accuracy (Right/Left)	69,9%	71%	82,8%	83,3%	100%
Accuracy(Inferior/Superior)	62,2%	67,6%	79,3%	83,3%	66,7%

*Technique used for a small number of patients.

Patients reported as clinical manifestations correlated to primary hyperparathyroidism: kidney stones, skeletal manifestations (osteoporosis, bone pains, fractures), neuropsychiatric and neurocognitive symptoms (asthenia, difficulty in concentration, irritability, anxiety, depression), acute pancreatitis. In 15 patients the diagnosis was made after the detection of high calcium and PTH serum levels, in absence of any manifestation related to the disease.

Patients underwent two different types of surgical procedures: MIVAP was performed in 33 cases (41.2%), while in 47 (58.7%) bilateral exploration was chosen. Adenomas located during surgery were, in order of frequency: lower right, lower left, upper left and upper right.

Each patient underwent a preoperative evaluation with different imaging techniques, for each of which positivity rate, sensitivity, positive predictive value and accuracy were calculated. The results of this analysis are described in Table II.

Positivity rate: percentage of cases in which the examination assessed the presence of the adenoma, independently of the correct or incorrect evaluation of the lateralization.

Sensitivity (right / left): sensitivity of correct identification of right or left lateralization of the adenoma.

Sensitivity (superior / inferior): sensitivity of correct identification of superior or inferior lateralization of the adenoma.

PPV: positive predictive value.

Accuracy (right / left): correct imaging technique identification of right or left lateralization of the adenoma.

Accuracy (superior / inferior): correct imaging technique identification of superior or inferior lateralization of the adenoma.

Sensitivity of neck US and dual phase scintigraphy were calculated separately in patients affected or not by thyroid disease of surgical interest. The aim of this was to evaluate a possible negative effect of thyroid pathology on the technique ability in the identification of parathyroid adenoma. Thyroid disease was related with a lower imaging sensitivity.

We have evaluated the concordance between the most frequently used imaging techniques in preoperative evaluation: neck US, dual phase scintigraphy and SPECT/CT. Our results showed that sonography and scintigraphy had a very high concordance in expressing left-right and upper-lower lateralization (Table IV). In

TABLE III - Impact of thyroid disease on preoperative imaging evaluation.

	Goiter presence	Goiter absence
US positivity	78,2%	78,9 %
Scintigraphy positivity	83,6%	78,6%
US sensitivity (right-left)	73,6%	70,6%
Scintigraphy sensitivity(right-left)	78%	76,9%

TABLE IV - Concordance between preoperative evaluation techniques

	Concordant cases	Negative Concordance	(Cohen's Kappa)	P value
Positivity US/SCINTIGRAPHY	65,7%	1	- 128	> 0,05
Positivity US/SPECT/CT	76%	0	- 119	> 0,05
Right/Left Location US/SCINTIGRAPHY	94,8%		0,892	< 0,05
Superior/inferior Location US/SCINTIGRAPHY	100%		1.000	< 0,05

TABLE V - Concordance / discordance of preoperative imaging and IOPTH

	PTH > 50% decrease ('10)	PTH < 50% decrease ('10)	P value
Positive findings US/scintigraphy concordance (37)*	34 (91,9%)	3 (8,1%)	> 0,05
Positive findings Sonography/scintigraphy discordance (22)*	19 (86,4%)	3 (13,6%)	
Right-left: US/scintigraphy concordance (34)	31 (91,2%)	3 (8,8%)	> 0,05
Right-left: US/scintigraphy discordance (1)	1 (100%)	0	

* Discordant (D) = positive examination / negative examination or both negative

* Concordant (C) = positive examination / positive examination

TABLE VI - Factors with possible impact on the cure rate

Variabile	Cure Rate	P Value
Age < 65	86,8 %	> 0,05
Age > 65	90,5 %	> 0,05
Sex F	85,7 %	> 0,05
Sex M	100 %	> 0,05
Positive US	90,9 %	> 0,05
Positive scintigraphy	87,2 %	> 0,05
Positive SPECT/CT	76 %	> 0,05

64 cases it was possible to find data on both sonography and scintigraphy used for preoperative evaluation, in 16 patients data were missing. On these 64 patients we obtained the following results: 41 positive concordant examinations, 22 discordant examinations and only 1 case with both negative results. In 25 cases neck US was associated with SPECT/CT with the following results: 19 cases with concordant positivity, 6 cases with discordant imaging and 0 cases with negative concordance. Intraoperative PTH serum levels (IOPTH) were correlated with patient outcomes and preoperative calcium and PTH levels. 50% decrease of PTH serum levels 10 minutes after adenoma resection was statistically correlated ($p < 0.05$) to patient's healing, defined by the normalization of calcium and PTH levels 6 months after surgery. In patients with a decrease of IOPTH levels, preoperative calcium and PTH serum levels were not significantly different ($p > 0.05$) from those patients in whom hormone concentration remained high. Therefore, pre-operative calcium and PTH levels seem not to influence IOPTH.

IOPTH levels were also correlated to preoperative findings in order to assess a correlation between concordant or discordant imaging and IOPTH levels decrease. From our analysis, no correlation emerged ($p > 0.05$).

POSSIBLE FACTORS INFLUENCING THE CURE RATE

On 59 patients out of 80, it was possible to collect follow up data in order to calculate the cure rate. We analyzed: age, sex, positive sonography, positive scintigraphy, positive SPECT/CT. None of these variables were correlated with the cure rate.

Follow-up data were also used to evaluate a possible correlation between healing, pre-operative and post-operative calcium, PTH serum levels. Mean preoperative calcium (11.1 ± 1.1) as well as PTH serum levels (211.7 ± 68.1) in patients considered cured were not statistically significant different ($p > 0, 05$) from those patients with persistent or recurrent disease (Calcium: 11.2 ± 0.3 ; PTH: 249.6 ± 137.5). Patients with recurrent or persistent disease were associated with mean postoperative calcium and PTH serum levels higher than those of patients considered cured (Calcium: 10 ± 0.6 VS 8.9 ± 0.9 ; PTH: 151 ± 54 VS 45 ± 30).

Finally, we evaluated the correlation between surgical approach (MIVAP or BNE) and patient's outcome: these parameters resulted independent ($p > 0.05$).

Discussion

Parathyroidectomy is the only definitive treatment for primary hyperparathyroidism. Traditionally, bilateral

neck exploration (BNE) was the gold standard procedure because of the possibility of visualization and evaluation of all parathyroid glands, also in cases of widespread hyperplasia and ectopic adenomas^{28,29}.

In recent decades, minimally invasive parathyroidectomy (MIP) has become a widespread surgical approach for treatment of pHPT, thanks to the improvement of preoperative localization imaging techniques and the use of IOPTH dosage. The advantages of this procedure are small incision size, reduction of post-operative pain, shorter surgical time and shorter hospitalization^[30]. The risk of post-operative complications, such as recurrent laryngeal nerve injury, post-surgical bleeding and hypoparathyroidism is lower than in BNE. Accurate preoperative adenoma localization is essential in minimally invasive parathyroid surgery to achieve a cure rate equal to that of BNE^{9,10,31}.

An optimal algorithm for preoperative evaluation in patients affected by hyperparathyroidism has not yet been determined¹⁹. The most use imaging techniques are neck ultrasound, dual phase scintigraphy with ^{99m}Tc-MIBI and SPECT/CT, according to the latest guidelines of the II Italian consensus conference²⁰.

A review by Lumachi et al.³³ on preoperative US and dual phase scintigraphy findings in patients with solitary adenoma, found a combined sensitivity of 95% versus 87% of scintigraphy and 80% of ultrasonography alone. At our Institution, sensitivity of neck US and scintigraphy were in the range described in literature, from 48% to 89% for ultrasound and from 61% to 100% for scintigraphy.

In our study, SPECT/CT has obtained the best results for almost all parameters, overcoming scintigraphy, and this last observation is due to the fact that SPECT/CT provides three-dimensional (3-D) topographic information and functional assessment of adenoma.

Guidelines, in fact, recommend its use in particular for the morphological study of ectopic glands. SPECT/CT is currently the preoperative exam with the highest identification rate (95%)¹⁵.

The use of 4D TC in recent publication is recommended for re-operative treatment of PHPT³⁴.

MRI and CT are second level techniques and are useful in cases of ectopic glands, persistent or recurrent pHPT and suspected carcinoma. CT results quite accurate to localize ectopic adenomas in the mediastinal site and to evaluate the possible spread of a carcinoma to surrounding organs. MRI, on the other hand, provides complementary information to scintigraphy for the ectopic sites, but its accuracy decreases in presence of concomitant thyroid nodules.

The excellent performance assessed by our study for these two-imaging techniques is probably due to the reduced sample of patients that underwent CT and MRI and does not justify their use as first choice methods.

Among the traditional methods, ultrasound has obtained the best positive predictive value and the worst in terms

of accuracy. Concordance between preoperative imaging techniques (ultrasound, scintigraphy, SPECT/CT) has led us to further evaluations. Sonography and scintigraphy seem to be extremely concordant concerning lateralization, right-left or superior-inferior. On the other hand, concerning the presence or absence of adenoma, neck US is often discordant with both scintigraphy and SPECT/CT. This finding reduces the total positive concordance, but on the other hand, it guarantees a very low number of cases with negative concordance, that means a missed finding by both imaging techniques.

Ultrasound-scintigraphy combination is suitable for preoperative evaluation as it guarantees, in almost all cases, a positive result from at least one of these two techniques.

The concomitant presence of parathyroid and thyroid disease is quite frequent, and the latter seems to decrease imaging accuracy in the study of parathyroid adenoma^{35,36}. Thyroid disorders of surgical interest (cysts, nodules, carcinomas, multinodular goiter, Basedow-Graves' disease) were found in 19 patients (23.75%) included in our study.

Our data have shown a minimal reduction in the sensitivity of right-left localization in both US and scintigraphy. Minimally invasive surgery has also led to the development and diffusion of the IOPTH. IOPTH dosage is recommended during OMIP (Open Minimally Invasive Parathyroidectomy) and MIVAP (Minimally invasive video-assisted parathyroidectomy)^{6,10,20}.

The correlation between decrease > 50% of IOPTH serum levels and healing was confirmed and indeed, PTH serum levels fall confirms the successful adenoma removal and the absence of other hypersecreting glands. In case of persistent high IOPTH serum levels, the surgeon has the possibility to choose the bilateral neck exploration or to set up a strict follow-up in case of a possible persistence of the disease.

The first intraoperative PTH guidelines¹⁹ recommended its use for minimally invasive approaches, while recent evidences suggest that in case of concordant preoperative imaging IOPTH dosage is not required also in minimally invasive parathyroidectomy^{20,22}. Preoperative calcium and PTH serum levels did not influence IOPTH values.

The correlation between variables as age, sex, positive sonography, positive scintigraphy, positive SPECT/CT, and the outcome of patients undergoing parathyroidectomy was evaluated.

A first correlation identified in our study has already been presented: the fall of the IOPTH correlates significantly with patient's healing.

In literature, some studies show that patients over 70 years have a greater risk of disease persistence or recurrence but in our experience we haven't identified this correlation. Pre- and post-operative calcium and PTH serum levels were analyzed by comparing the mean values in patients considered healed and in those with persi-

stent or recurrent disease. Our results are concordant with literature: preoperative calcium and PTH serum levels are not different in the two patient groups, while not healed patients had higher post-operative calcium and PTH serum parameters can be considered predictors of surgical treatment failure.

Finally we have not reported a correlation between the surgical procedure chosen and the patient's outcome.^{37,38}

Conclusion

The combination of neck ultrasound and dual phase scintigraphy is suitable for preoperative evaluation since it guarantees, in almost all cases, a positive finding from at least one of the two techniques.

New preoperative imaging techniques, today not routinely applied, can be used in case of relapse of pHPT. The concomitant presence of thyroid disease might also decrease the results as in our patients.

This research did not receive any specific grant from funding agencies in the public, commercial or not for profit factors.

Riassunto

L'iperparatiroidismo primario (pHPT) è un disturbo endocrinologico caratterizzato da un'eccessiva secrezione di paratormone. L'approccio mini-invasivo è diventato un metodo chirurgico diffuso per il trattamento del pHPT grazie al miglioramento delle tecniche di imaging per la localizzazione preoperatoria della ghiandola e grazie alla pratica del dosaggio intraoperatorio di PTH (IOPHT). Discutiamo qui i risultati di diverse tecniche di imaging.

Per questo abbiamo condotto un'analisi retrospettiva di 80 pazienti sottoposti a intervento chirurgico per iperparatiroidismo primario nel periodo tra il 01/01/2012 e il 28/02/2018 e abbiamo concentrato la nostra raccolta di dati sullo studio preoperatorio, sulle osservazioni intraoperatorie e sui dati del follow-up. Abbiamo valutato la concordanza tra i risultati delle tecniche di imaging più utilizzate, la concomitanza di patologia tiroidea e la IOPHT. La SPECT-CT ha mostrato i migliori risultati in termini di positività (93,1%), sensibilità (88,9%) e precisione (82,8%). L'ecografia del collo è risultata avere il miglior valore predittivo positivo (94,4%). La riduzione della IOPHT era correlata alla guarigione dei pazienti ($p < 0,05$). Età inferiore a 70 anni, livelli sierici post-operatori di calcio e PTH sono risultati correlati a una maggiore possibilità di guarigione ($p < 0,05$).

In conclusione la combinazione tra ecografia e scintigrafia risulta adatta per la valutazione preoperatoria e la SPECT/CT conferma il miglior esame aggiuntivo; la presenza di patologie tiroidee diminuisce la sensibilità. Il IOPHT è un importante elemento prognostico positivo per la guarigione.

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