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Technical reports and immediate results from the initial experience

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The intraoperative use of the mini-gamma camera(MGC) in the surgical treatment of primary hyperpathyroidism. Technical reports and immediate results from the initial experience

INTRODUCTION: *The treatment of primary hyperparathyroidism consists almost exclusively in the parathyroidectomy. The preoperative imaging (ultrasonography, 99mTc sestamibi scan) can allow to localize the pathologic gland and perform minimally-invasive focused techniques, but in presence of ectopic or intrathyroidal glands, parathyroid hyperplasia or coexistent thyroid disease, the sensitivity of these imaging techniques worsens. The present study shows a new technique of preoperative scintigraphic imaging and describes the early applications of this technique investigating if it is useful in improving the localization of the pathologic parathyroid.*
METHODS: *Five female patients were enrolled in the study. In all cases, we performed a parathyroidectomy using a systematic recognition of the four parathyroid glands under intraoperative PTH monitoring, adding the use of the intraoperative gamma camera to usual surgical procedures. We evaluate the concordance of the results of the intraoperative gamma camera with the preoperative diagnosis, the intraoperative PTH monitoring and the intraoperative findings. Moreover, the results of the treatment one month after the surgical procedure were also considered.*
RESULTS: *The results of intraoperative scintigraphy were always concordant with intraoperative findings. The intraoperative PTH monitoring and the results of the follow-up confirmed the completeness of the excision, at least in a short period of observation.*
CONCLUSIONS: *The intraoperative gamma camera could help to improve the localization of a pathologic parathyroid gland. These results could be useful in improving the results of minimally invasive surgery as well as "difficult" situations.*

KEY WORDS: Intraoperative minigamma camera, Parathyroidectomy, Primary hyperparathyroidism, Parathyroid scintigraphy

Introduction

The treatment of primary hyperparathyroidism (PHPT) is almost exclusively the excision of the gland(s) responsible of the parathormone (PTH) hyperproduction and subsequently of the hypercalcemia [1,2]. This surgical approach consists of the systematic recognition of the 4 parathyroid glands with the aim to identify and remove the enlarged one(s) owing to hyperplasia, adenoma or, rarely, carcinoma [3,4]. This procedure is successful in over 95% of cases [3]. However, the new imaging techniques for the localization of pathologic gland(s) allowed the appearance of less invasive and/or focused surgical procedures [5-7]. Nowadays the association of high resolution small parts ultrasonography (US) and 99mTC sestamibi

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scan (MIBI) is the gold standard for the preoperative localization of enlarged parathyroid glands [8-10], and it cannot be given up in anticipation of a minimally invasive focused technique [5,6]. The sensitivity of this diagnostic protocol varies between 69 and 96%, being affected negatively in the presence of ectopic or intrathyroidal hypersecernent glands, parathyroid hyperplasia or coexisting thyroid disease [10,11]. Anyway, a successful detection and localization of the enlarged gland(s) responsible for the hyperparathyroidism, in the preoperative period as well as in the intraoperative one assure good results in terms of low recurrence/persistence rate and operative time [12,13]. Conversely, the new minimally-invasive techniques of parathyroidectomy made the localization of parathyroids into a great relevance [5,10].

With the aim to identify a tool capable of detect and localize the enlarged and hyperfunctioning parathyroid glands during the surgical procedure, we used a new imaging tecnique of intraoperative scintigraphy with the MGC. With the present study we set ourselves the objective of illustrate the technical dictates and describe the early applications of this technique at our institution in the treatment of PHPT.

Materials and Methods

From September the 10th, to November the 22th 2014, 5 female patients suffering from PHPT were enrolled at our institution. The median age of the patients was 65 years (min.: 50; max.: 73). The present case series has been prospectively examined from the day of the enrollment until 30 days after parathyroidectomy. The patients were studied in coordination with the Nuclear Medicine Unit, the Endocrinology, the Pathology and the Clinical Analysis Institutional Services. All the patients underwent a preoperative ultrasonography, carried out at our institution from an experienced operator of the team (one between G.S. and P.R.) with an ultrasound device endowed with a linear probe of 7-10 MHz. Moreover, in all cases a parathyroid scintigraphy was performed using the single tracer, double-phase protocol.

A dose of 370 MBq (10 mCi) of 99mTc-MIBI (Technemibi, Mallinkrodt) was injected intravenously 15 minutes (early scan) and two hours (late scan) before the planar acquisition of the images of the head and mediastinum.

The late acquisition showed the wash out of the radiopharmaceutical from the thyroid and the persistence of the parathyroid image.

We decided to perform the initial diagnostic scan and surgery on different days using low doses of radioisotope, in order to minimize the radiation exposure to surgical staff in the operating room. All preoperative imaging tests were examined from the endocrinologist, the nuclear physician and the surgeon.

All the patients suffering from PHPT, referred at our Institution during the period of reference, were enrolled in the study, including those with non-concordant preoperative imaging, suspected multiglandular disease or concomitant thyroid disease. In this last occurrence, the patients were scheduled to perform a completion or total thyroidectomy, as needed. All the patients accepted to participate in the present study by signing an informed consent. Institutional Ethics Committee approval was also obtained. In order to asses the value and the usefulness of the MGC intraoperative scintigraphy, we carried out all surgical procedures following the usual protocol we would have applied in each specific situation. As a difference, we added the use of the MGC to the usual surgical proceeding.

Description of the Equipment

The instrument used for performing the intraoperative scintigraphy was the *Sentinella 102*® (GEM Imaging S.A., Valencia, Spain), a transportable high-definition Gamma Camera integrated to a dedicated software and a complementary wireless gamma-probe. These elements are located into a trolley endowed with an electromechanical arm that allows an accurate positioning of the gamma camera over the operative field. This device adds to the outcomes of the traditional gamma probe (pulse of sound and radioactivity value, CPS) an accurate spatial mapping of the radioactive tissues, generating images quite similar to the images of a conventional scintigraphy. The Sentinella 102® hand-held MGC has a head module composed of a high-resolution collimator, a continuous CsI (Na) scintillating crystal, a flat panel position-sensitive photomultiplier tube. The gamma camera dimensions are 14x8x9 cm, weighs 1 kg and has a computerized system with 2 screens (touch screen monitor on the surgeon side), enabling the simultaneous display of scintigraphic images, for both nuclear physician and surgeon.

Due to the use of a pin-hole collimator, this small gamma camera has a variable Field Of View (FOV) according to the aperture and to the distance from the body to the pin-hole. This device offers 20x20 cm field of view (FOV) at a distance of 15 cm and high sensitivity 5 cm far from the surgical field (110 cpm/μCi using 2,5 mm pinhole collimator, 233 cpm/μCi using 4 mm pinhole collimator), which allows quick imaging acquisition. Its ability for localization of small hot radiation regions is improved by means of the laser positioning system (LPS), a red light made up of two laser crossed lines, for reference position establishment between body and gamma image. This LPS marks the body situation for the central zone of the screen and allows marking the cutaneous point corresponding to maximal radiation or confirming if the scintigraphy point of maximal and uptake matches to the suspected nodule.

Description of the Technique

On the day of the surgery, in the operating room, after anaesthesia, the nuclear physician administered an intravenous dose of 185 MBq (5 mCi) of 99mTc-MIBI.
Four scintigraphic images of the neck were acquired in the anterior projection, placing the collimator at a distance of 15 cm: (1) before skin incision, 15-20 minutes after the injection; (2) after pathologic parathyroid location; (3) after gland excision and (4) ex vivo imaging of the excised material. The last images certified the isotope uptake by the specimen, confirming that the excised material was truly responsible for the initial detection, as well as the absence of the previous hot spot in the surgical field.

Patients Assessment

The collected data concerning the present case series were: age, sex, pathology (regarding both thyroid and parathyroid glands), preoperative calcium values, preoperative U.S. and scintigraphy, intraoperative findings on surgical exploration. Blood samples were collected, with the aim to perform an i.o. PTH monitoring: at the preoperative time; at parathyroid excision; 5 minutes after excision; 20 minutes after excision. An i.o.PTH drop ≥ 50% and at all events under the threshold limiting value (65 pg/ml) was considered successful. A resident carried the 4 blood samples at the Clinical Analysis Institutional Service, were the PTH dosage was performed. The MGC scintigraphy, carried out as described above, was examined with the aim to highlight concordance or discordance with preoperative imaging and i.o.PTH monitoring. Finally, the follow-up data (calcium and PTH values 1 month after surgical operation) were collected.

Results

The details concerning the case series are shown in the Table I.
Concerning the case n. 1, we want to underline the discordance of the preoperative imaging in terms of level. In the case n. 2, the MIBI showed a posterior captation on the left side, that rather oriented for a superior parathyroid gland. In the case n. 3, no level had been specified with U.S. nor with MIBI. In the case n. 4 (Figs. 1-4) U.S. had been negative, because of the anatomic position of the parathyroid gland (Fig. 5). Finally, in the case n. 5 the preoperative imaging oriented for a multiglandular disease, with a discordance concerning the superior glands, that were normal at the surgical exploration, as deduced with intraoperative minigamma camera. In all, the use of the intraoperative gamma camera showed that in all cases the results of intraoperative scintigraphy were concordant with the intraoperative findings, as confirmed from the i.o. PTH dosage and the follow-up, at least in a short period of observation.

Table I - *Characteristics of the patients enrolled in the study*

N.	Age	Pathology	Preop. Ca++	Preop PTH	Ultrasonography	MIBI	IO PTH	I.O scintig.	I.O. finding	follow-up	Hystol.
1	65	PHPT	13.3	684.5	R., post, super. cm. 2,8 X 1,7	R., mid-infer.	571.4 776.5 133.5 38.6	PIII Right	PIII Right	Ca++: 8.9 PTH: 24.4	parathyroid carcinoma
2	50	persist. PHPT + goiter	11.7	469	L., mid-infer. cm 2,5 X 1,5	L., post.	256.8 88.1 48.2 15.2	PIII Left	PIII Left	Ca++: 9.23 PTH: 68	parathyroid adenoma left PTmC
3	62	PHPT + TMNG	11.08	192.9	L. (?) cm. 2,6 X 1,2	L. (?)	212.9 103.2 30.2 24.7	PIV Left	PIV Left	Ca++: 8.52 PTH: 9.1	parathyroid adenoma multinodular goiter
4	73	PHPT + TMNG	14.2	421.8	Negative	R. infer.	164.6 119.5 48.7 29.6	PIV Right	PIV Right	Ca++: 8.6 PTH: 19.8	parathyroid adenoma multinodular goiter
5	67	PHPT + TMNG	10.7	141.7	R., infer, cm. 1.7 X 1.3 R., Super., cm. 0.8 X 0.8	R., infer L., super.	122.8 71.1 16.0 12.3	PIV Right	PIV Right	Ca++: 9.1 PTH: 34.5	parathyroid adenoma multinodular goiter

Legend: L = left; R = right; post = posterior; super. = superior; persist. = persistent; TMNG = toxic multinodular goiter; PTmC = papillary thyroid microcarcinoma.

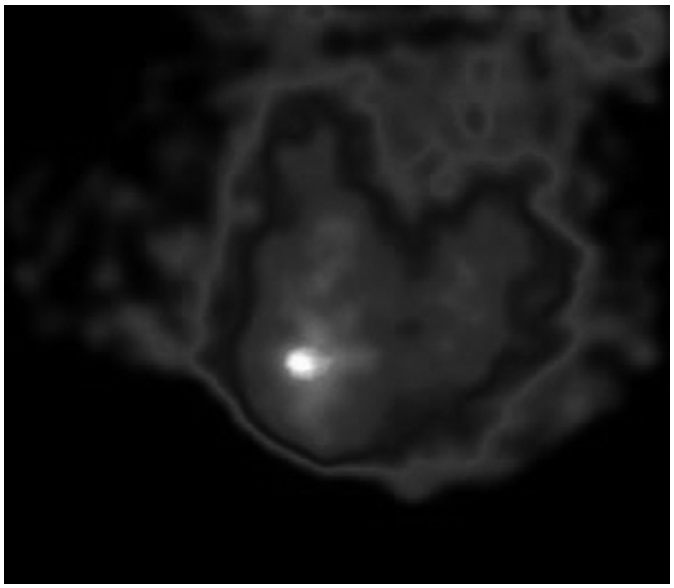

Fig. 1: Image acquired twenty minutes after administration of 99mTc-MIBI, before skin incision.

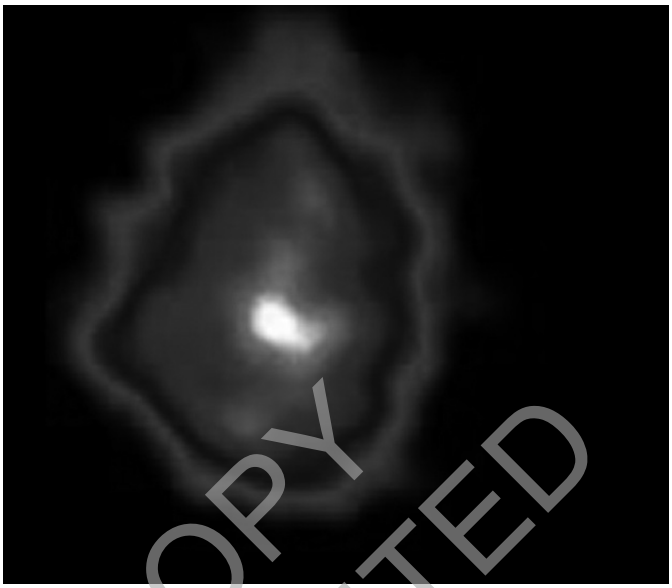

Fig. 3: Ex vivo imaging of the excised materials.

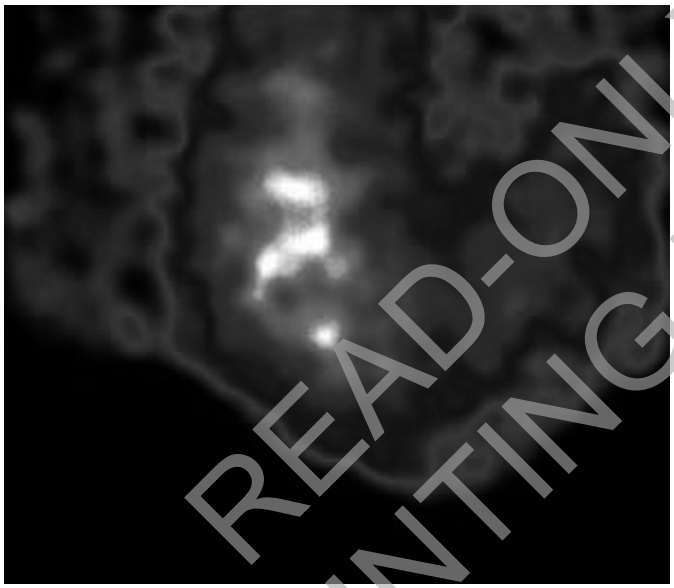

Fig. 2: Acquisition performed 90 minutes after administration of the radioisotope, after parathyroid excision.

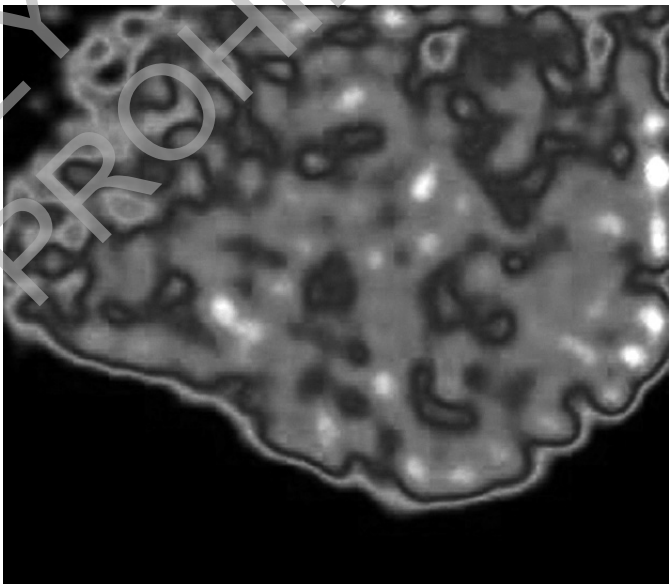

Fig. 4: Image performed after parathyroidectomy and thyroidectomy.

Discussion

The PHPT is the third most common endocrine disease, after thyroid disorders and diabetes; it mainly affects women in post-menopausal period [1,5,14]. Its natural history concerns the impairment of several functions [15-18], with a relevant impact in quality of life [19] and even lethal consequences [18,20,21]. The surgical approach is the only definitive treatment of PHPT, being the medical treatment a palliation of hypercalcemia effects as a bridge to the definitive treatment or in patients in whom surgery is not indicated (severe comorbidities and/or advanced age) [1-5,21,22]. The bilateral cervical neck exploration is the standard approach, since the likelihood of a multiglandular disease (MGD) is 15-25% [23]. The development of efficacious imaging techniques (high resolution U.S., MIBI) improve the diagnosis of localization in single-gland disease, but these techniques have some limitations in case of multiglandular disease, as well as coexistent thyroid disease or ectopic pathologic

Fig. 5: Surgical specimen: the right superior parathyroid gland (P IV) and the thyroid (multinodular toxic goiter). The surgical exploration showed the parathyroid glided along the prevertebral plane, just below the limit between the neck and the thorax, in the superior posterior mediastinum.

parathyroid gland [17,23,24]. In order to decrease the mistakes in localizing pathologic gland in the presence of coexistent thyroid disease some authors suggest a dual tracer (Tc99m-sestamibi - Tc99m-pertechnetate) scintigraphy [25,26], but this technique showed some limitations in case of reduced thyroid uptake, superimposition of thyroid and parathyroid images and incidental movements of the patients during the image acquisition (10, 27). The single positron-emission computed tomography (SPECT) has been advocated in order to improve the quality of images during parathyroid scintigraphy, their accuracy and sensitivity [25,27-28]. Although the advantages of this technique, its cost is elevated, then its indications are limited to "difficult" cases, such as coexistence of thyroid disease, persistence or recurrence of hyperparathyroidism [10]. In addition to the improvement of preoperative imaging, the recent advances in the intraoperative diagnosis facilitate the detection and the localization of pathologic parathyroid glands. Even if the intraoperative monitoring of the PTH (i.o.PTH) is not universally accepted, it is an efficacious tool to prevent the persistence, especially in presence of MGD [29-30] as well as in secondary hyperparathyroidism [31]. The use of the gamma-probe is an useful tool to improve the localization of an hyperfunctioning parathyroid gland, especially in ectopic and/or deep (retroesophageal) gland [6,10,32,33]. The use of MGC in theatre, during surgical procedures is a step forward, because it provides intraoperative and postoperative high-quality scintigraphic imaging of hyperfunctioning parathyroids. In the present study the technique showed an optimal spatial resolution that allowed a reliable localization in terms of side (left-right) as well as level (superior/inferior).

Conclusions

To date, the intraoperative use of MGC in primary hyperparathyroidism is the only tool that allows to obtain a suitable detection and a spatial localization of the pathologic parathyroid gland(s). No false results (neither positive, nor negative) have been observed in our short case series. We observed an unchanging overlap in terms of results compared to intraoperative findings corroborated from the results of the i.o.PTH. Moreover, its use is not dedicated exclusively to parathyroid surgery, but it can also be used in several applications of surgical oncology: it makes its use acceptable in terms of operating expenses. Finally, the features of the technique forebode that it could be an useful and reliable tool in improving the results of minimally invasive surgery as well as "difficult" situations, such as recurrent/persistent hyperparathyroidism, ectopic, intrathyroidal or posterior gland, multiglandular disease. In this perspective, a larger experience is needed for confirming these assumptions.

Riassunto

Il trattamento dell'iperparatiroidismo primario è quasi esclusivamente chirurgico e consiste nell'esplorazione sistematica delle quattro ghiandole con asportazione di quella(e) patologica(e). Le più moderne tecniche di diagnosi (ecotomografia, scintigrafia 99 mTc sestamibi), migliorando le possibilità di individuare la ghiandola responsabile della malattia, consentono l'esecuzione di tecniche mini-invasive quando vi è concordanza tra i risultati delle due tecniche, ma la sensibilità di tali indagini è inficiata dalle ectopie ghiandolari, da paratiroidi intratiroidee, da malattia multighiandolare o dalla contemporanea presenza di malattie tiroidee. Il presente studio illustra una nuova tecnica di imaging scintigrafico intraoperatorio ed indaga sulla sua possibilità di migliorare la localizzazione intraoperatoria della paratiroide patologica. A tal fine, 5 pazienti sono state sottoposte a tale metodica, tutte trattate con paratiroidectomia previa esplorazione completa delle quattro ghiandole con tecnica tradizionale, con monitoraggio intraoperatorio del paratormone. Alla tecnica convenzionale è stato aggiunto l'impiego della gamma camera intraoperatoria. Abbiamo valutato la concordanza dei risultati di tale esame con i dati dell'esplorazione chirurgica e con il dosaggio intraoperatorio del paratormone. In tutte e 5 le pazienti si è osservata una perfetta concordanza tra la localizzazione della ghiandola patologica con la scintigrafia intraoperatoria e l'esplorazione chirurgica, ed il dosaggio intraoperatorio del paratormone ha confermato i dati. Anche il follow-up ad un mese ha confermato l'eradicazione della malattia. La gamma camera intraoperatoria sembra quindi poter migliorare le possibilità di localizzazione della ghiandola responsabile dell'iperparati-roidismo primario, favorendo l'impiego di tecniche mini-invasive e migliorando i risultati dinanzi a casi "difficili".

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Commento e Commentary

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L'iperparatiroidismo primitivo è nella maggioranza dei casi correlato ad un adenoma.
La medicina nucleare rappresenta un importante ed irrinunciabile aiuto al fine della localizzazione dell'adenoma. Infatti consente una ablazione mirata. Naturalmente l'avvenuta ablazione mirata è confermata mediante il dosaggio intraoperatorio del PTH.
La possibilità di valutare la presenza di una o più paratiroidi iperfunzionanti mediante la diagnostica per immagini radioisotopica rappresenta un valido ausilio ma presuppone la possibilità di beneficiare di un adeguato supporto tecnologico ed organizzativo.
Ortega e coll. avevano proposto la utilizzazione di una mini gamma camera nel 2007 al fine di attuare una paratiroidectomia mini-invasiva. Questi Autori confermavano il successo della paratiroidectomia mediante la scomparsa della captazione radioisotopica dopo l'ablazione della paratiroide iperfunzionante e completavano la conferma della riuscita dell'atto chirurgico mediante il controllo del PTH intraoperatorio.
Scerrino e coll. riportano la loro esperienza con la mini gamma camera nel trattamento chirurgico di cinque casi di iperparatiroidismo primitivo. Questi Autori evidenziano che la diagnostica per immagini mediante tecnologia radioisotopica realizzata con l'ausilio di una mini gamma camera nel corso dell'intervento chirurgico facilita la localizzazione della ghiandola paratiroidea patologica e ne conferma l'ablazione. La definitiva conferma del successo terapeutico è stata ottenuta mediante il dosaggio intraoperatorio del PTH.
Ritengo che la mini gamma camera rappresenti un valido ausilio integrativo al fine del raggiungimento del successo terapeutico ma che allo stato attuale non si può rinunciare alla valutazione intraoperatoria del PTH per la conferma dell'asportazione del tessuto paratiroideo patologico.

* * *

Primary hyperparathyroidisms are, in the majority of cases, related to a single adenoma.
The improved accuracy of nuclear medicine techniques represents an important and irreplaceable help for the demonstration and the localization of the adenoma. This permits a focused ablative therapy. Of course, the "focused" surgery has to be completed by the intraoperative confirmation of PTH reduction.
The possibility to evaluate the presence of hyperfunctioning parathyroid glands through nuclear medicine imaging is particularly useful and needs an adequate technological and organisational support.
Ortega and coll. have proposed the use of miniature gamma camera in 2007 in order to perform a minimally invasive parathyroidectomy. These Authors have confirmed the success of parathyroidectomy by proving the absence of positive radioactivity after the resection and by performing an intraoperative assay of PTH.
Scerrino and coll. report their experience with miniature gamma camera in the treatment of five cases of primary hyperparathyroidism. These Authors underline that this nuclear medicine technique facilitates the intraoperative localization of the pathological parathyroid gland and confirm that the intraoperative assay of PTH is irreplaceable in order to prove an efficient ablation of the pathological parathyroid.
We believe that using intraoperative nuclear medicine techniques (with gammaprobe or miniature gamma camera) represents an integrative possibility for the achievement of therapeutic success. Notwithstanding, especially if it's not possible to resort to nuclear medicine techniques, the help of intraoperative assay of PTH is undeniable.

References

Ortega J, Ferrer-Rebolleda J, Cassinello N, Liedo S: *Potential role of a new hand-held miniature gamma camera in performing minimally invasive parathyroidectomy*. Eur J Nucl Med Mol Imaging, 2007; 34:165-69.