ΠΡΩΤΟΤΥΠΗ ΕΡΓΑΣΙΑ

Preoperative localization of parathyroid glands in secondary hyperparathyroidism and concomitant thyroid disease

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^{99m}Tc-sestamibi and ultrasound are the most commonly used methods for the preoperative localization of parathyroids in patients with secondary hyperparathyroidism. The aim of this study was to assess the value and usefulness of parathyroid preoperative localization in secondary hyperparathyroidism, in the presence of coexistent thyroid disease.

Between 1996 and 1998, seventy two 72 parathyroidectomies for secondary hyperparathyroidism were performed. In 10 patients we found concomitant thyroid disease (14%). For the preoperative localization we used ultrasound and ^{99m}Tc-sestamibi scan.

Ultrasound revealed 19 parathyroid glands (50%) out of the 38 that were surgically removed. Their mean weight was 0.738 gr vs. 0.438 gr of those not detected (p=0.21) and the mean size was 1.221 cm vs. 0.973 cm (p=0.21) respectively. ^{99m}Tc-sestamibi demonstrated 17 glands (45%) with a mean weight of 0.836 gr vs. 0.387 gr of the glands not demonstrated (p<0.05) and a mean size of 1.294 cm vs. 0.938 cm (p<0.05) respectively. Two glands were not found. Only 10 parathyroid glands (26.3%) were identified simultaneously by both ultrasound and ^{99m}Tc-sestamibi (mean size 1.38 cm and mean weight 0.991 gr). Ultrasound demonstrated the superimposed thyroid disease in all 10 patients (100%), while ^{99m}Tc-sestamibi only in 3 (33%). The histology of the parathyroids was predominantly nodular hyperplasia in those glands detected with ^{99m}Tc-sestamibi. Nodular goiter was the predominant lesion of the thyroid gland.

Both studies, when they are used alone, have shown relatively low sensitivity (45% with ^{99m}Tc-sestamibi and 50% with ultrasound) in detecting parathyroid glands in secondary hyperparathyroidism and concomitant thyroid disease. Ultrasound scan can give information for the thyroid disease and it can be the first and sometimes the only study in every patient with secondary hyperparathyroidism undergoing neck exploration for a first time.
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Secondary hyperparathyroidism is a common complication in uraemic patients and in mild forms can be managed conservatively. Haemodialysis prolongs these patients' lives and finally the disease becomes uncontrollable under medical treatment. The only way to avoid complications like osteodystrophy, vessel and soft tissue calcification, is surgical removal of the glands. It is estimated that about 5% of patients with chronic renal failure treated with long-term dialysis will require surgery for secondary hyperparathyroidism [1].

For a successful operation, two important elements are required, first an experienced surgeon and second, preoperative localization of parathyroid glands. While there is no doubt about the value of the former element, much skepticism exists regarding the preoperative localization of parathyroid glands [2].

^{99m}Tc-sestamibi scintigraphy is more sensitive than ultrasound in primary hyperparathyroidism. In patients with secondary hyperparathyroidism however, the sensitivity is low and usually around 55% [3]. Ultrasound scan has a similar sensitivity

as well [4]. Patients with secondary hyperparathyroidism will undergo total parathyroidectomy and auto- transplantation in most of the cases. Remembering the low sensitivity of ^{99m}Tc-sestamibi and ultrasound and the anyway necessary bilateral neck exploration one cannot but wonder whether these patients actually require any preoperative localization study or not. The presence of thyroid disease may result in false positive findings and finally these localization studies may not offer any practical benefit to a patient undergoing neck exploration for a first time. In this retrospective study we tried to evaluate the reliability and usefulness of ^{99m}Tc-sestamibi and ultrasound in patients with secondary hyperparathyroidism and coexistent thyroid disease.

Subjects and Methods

Between 1996 and 1998 we performed 72 parathyroidectomies for secondary hyperparathyroidism. Ten of these patients had superimposed thyroid disease (3 males, 7 females, mean age 54 years, range 23-67). Nine patients were on long-term dialysis for about 6.5 years (range 3-11). One was a renal transplant patient. His hyperparathyroidism did not improve and finally he underwent parathyroidectomy 2 years following transplantation. None of the patients presented any symptoms related to thyroid disease nor they had any history of neck exploration.

The indication for parathyroidectomy was based on clinical and biochemical evidence, that is bone aches, myalgia, pruritus, increased intact parathyroid hormone (iPTH) and / or increased serum calcium.

For the preoperative localization we used ^{99m}Tc-sestamibi imaging and ultrasound. In ^{99m}Tc-sestamibi scintigraphy the patients were injected with 20 mCi of ^{99m}Tc-sestamibi.

Images were obtained at 10-15 minutes (early or thyroid phase) and 2-3 hours later (delayed or parathyroid phase). Increased and persistent uptake on delayed phase was considered pathological.

Ultrasonography was performed using a 7-10 MHz transducer. Longitudinal and transverse images of the neck were obtained from the level of the mandibular angle to the sternal notch. A hypoechoic mass adjacent to, or inferior to thyroid was considered to represent pathological parathyroid gland.

All the patients underwent bilateral neck exploration and total parathyroidectomy. This was followed by autotransplantation in the subcutaneous tissue of the anterior abdominal wall provided that all four glands were identified. Post-operatively the patients were followed up for an average of 24 months (range 6-46).

All values are given as mean±standard deviation (M±SD). Comparisons were made using the Mann-Whitney U test and $P<0.05$ was considered significant.

Results

Patient characteristics are as outlined in Table 1. Preoperatively the mean iPTH was 1250 ng/l (range 345-1927, normal value 10-58). Seven patients were hypercalcaemic and the other 3 normocalcaemic. The mean serum calcium was 10.8 mg/dl (range 13.2-9.2, normal value 8.1-10.4). Ultrasound scan revealed 19 glands (50%) out of the 38 that were surgically removed and ^{99m}Tc-sestamibi 17(45%). Only 10 parathyroid glands (26.3%) were identified simultaneously by both ultrasound and ^{99m}Tc-sestamibi, while 26 glands (68.5%) were localized by adding the positive results of the two studies. We were not able to find two glands in spite of meticulous exploration. These glands were not detected preoperatively either. We performed autotransplantation in 8 patients. In the other 2, that the fourth parathyroid gland was not found autotransplantation was not performed.

Histologically all the parathyroid glands showed hyperplasia, diffuse or nodular, from oxyphill, chief or clear cells. We did not find any particular type of cells in those glands that were localized with ^{99m}Tc-sestamibi. We noticed however that in patient 1 and patient 3, (table 1) where ^{99m}Tc-sestamibi did not reveal any gland, the histology showed diffuse hyperplasia. In patient 4, where all the parathyroid glands were identified, the histology showed nodular hyperplasia.

As far as thyroid pathology is concerned nodular goiter was found in 8 patients, diffuse goiter in 1 and adenomatous goiter in 1. For the thyroid disease we performed 2 left lobectomies, 2 right lobectomies, 5 subtotal thyroidectomies and 1 total thyroidectomy.

The mean weight of all the 38 parathyroid glands was 0.588±0.830 gr and the mean size 1.097±0.584 cm (Table 2). The 17 glands identified with ^{99m}Tc-sestamibi had a mean weight of 0.836±1.024 gr. and a mean size of 1.294±0.541 cm while the 21 not localized had a mean weight of 0.387±0.402 gr. and a mean size of 0.938±0.536 cm ($p<0.05$). Regarding the 19 glands localized with ultrasound the values were 0.738±0.999 gr. and 1.221±0.635 cm respectively. Those not localized by ultrasound had a mean weight of 0.438±0413 gr. and a mean size of 0.973±0.458 cm ($p=0.21$).

In 8 of the 19 glands localized by ultrasound the ultrasonographer estimated their size pre-operatively. Their mean size was 1.575±0.489 cm but after surgical removal this was found to be 0.937±0.609 cm ($p<0.05$).

Table 1. Characteristics of patients

	Age	Parathyroids localized by US	Parathyroids localized by Sestamibi	Size after surgical removal	Weight after surgical removal	History of Parathyroids	History of Thyroid	Operation for Thyroid	Thyroid disease found by US	Thyroid disease found by Sestamibi
Patient 1	56	*RU:-, *RL:- *LU:-, *LL:-	RU:-,RL:- LU:-, LL:-	1.4, 1.5 cm 1 cm, (-)	0.33 ,0,352 gr 0,295 gr, (-)	Diffuse hyperplasia-chief and clear cells	Nodular goiter	Left Lobectomy	+	-
Patient 2	45	RU:1.4, RL:1.9 cm LU:1.4, LL:1.3 cm	RU:+, RL:- LU:+, LL:-	1.5 , 0.5 cm 1.5, 1.5 cm	0.650 , 0.165 gr 0.530, 0.355 gr	Nodular hyperplasia-oxyphill and clear cells	Nodular goiter	Subtotal Thyroidectomy	+	+
Patient 3	67	RU:+, RL:- LU:-, LL:+	RU:-, RL:- LU:-, LL:-	2.3, 0.8 cm 1.5, 1.5 cm	1.3, 1.25 gr 0.98 , 0.98 gr	Diffuse hyperplasia-chief, clear nd oxyphill	Adenoma-tous goiter	Right Lobectomy	+	-
Patient 4	67	RU:-, RL:- LU:-, LL:+	RU:+, RL:+ LU:+, LL:+	1.5, 1,5 cm 1.4, 1.8 cm	0.96, 0.925 gr 1.23, 4.46 gr	Nodular hyperplasia from oxyphill cells	Nodular goiter	Right Lobectomy	+	+
Patient 5	62	RU:1, RL:2.5 cm LU:1.2, LL:1.9 cm	RU:-, RL:+ LU:-, LL:+	0.5, 1.5 cm 0.2, 0,3 cm	0.128, 0.634 gr 0.051, 0.065 gr	Nodular hyperplasia-oxyphill and chief cells	Nodular goiter	Left Lobectomy	+	-
Patient 6	23	RU:+, RL:- LU:+, LL:-	RU:+, RL: - LU:+, LL:-	1.1cm , 0.8 cm 2, 0.5 cm	0.45, 0.22 gr 1.74, 0.088 gr	Nodular hyperplasia-oxyphill and chief cells	Nodular goiter	Subtotal Thyroidectomy	+	-
Patient 7	59	RU:-, RL:- LU:+, LL:-	RU:- RL:+ LU:-, LL:-	1, 1.2 cm 1.2, 0.2 cm	0.183, 0.380 gr 0.450, 0.054 gr	Diffuse hyperplasia-oxyphill and chief cells	Nodular goiter	Total Thyroidectomy	+	+
Patient 8	56	RU:+, RL:- LU:-, LL:+	RU:-, RL:- LU:+, LL:+	1.1 cm, (-) 1.1, 1.4 cm	0.656 gr, (-) 0.506, 0.658 gr	Nodular hyperplasia-oxyphill and clear cells	Diffuse goiter	Subtotal Thyroidectomy	+	-
Patient 9	57	RU:+, RL:+ LU -, LL:-	RU:+, RL:- LU:-, LL:+	1, 0.6 cm 0.5, 0.4 cm	0.43 , 0.095 gr 0.063 ,0.054 gr	Nodular and diffuse hyperplasia from clear and oxyphill cells	Nodular goiter	Subtotal Thyroidectomy	+	-
Patient 10	51	RU:+, RL:- LU:-, LL:-	RU:+, RL:+ LU:-, LL:-	1, 0.8 cm 0.5, 0.6 cm	0.30, 0.25 gr 0.07, 0.09 gr	Nodular hyperplasia from oxyphill cells	Nodular goiter	Subtotal Thyroidectomy	+	-

*RU: Right Upper, *RL: Right Lower, *LU: Left Upper, *LL: Left Lower

Table 2. Mean weight and size of parathyroid glands(n= number of glands)

Mean weight of all parathyroid glands (n=38):	0.588±0.830 gr
Mean size of all parathyroid glands (n=38):	1.097±0.584 cm
Mean weight of parathyroids detected with ^{99m}Tc-sestamibi (n=17):	0.836±1.024 gr
Mean weight of parathyroids not detected with ^{99m}Tc-sestamibi (n=21):	0.387±0.402 gr
Mean size of parathyroids detected with ^{99m}Tc-sestamibi (n=17):	1.294±0.541 cm
Mean size of parathyroids not detected with ^{99m}Tc-sestamibi (n=21):	0.938±0.536 cm
Mean weight of parathyroids detected with ultrasound (n=19):	0.738±0.999 gr
Mean weight of parathyroids not detected with ultrasound (n=19):	0.438±0.413 gr
Mean size of parathyroids detected with ultrasound (n=19):	1.221±0.635 cm
Mean size of parathyroids not detected with ultrasound (n=19):	0.973±0.458 cm
Mean size of parathyroids estimated with ultrasound (n=8):	1.575±0.489 cm
Mean size of parathyroids after surgical removal (n=8):	0.937±0.609 cm
Mean size of parathyroids detected by both studies (n=10):	1.38±0.597 cm
Mean weight of parathyroids detected by both studies (n=10):	0.991±1.295 gr

Ten glands (26.3%) were identified by both ultrasound and sestamibi scintigraphy. Their mean size was 1.38±0.597 cm and the mean weight was 0.991±1.295.

The sensitivity and specifisity of ultrasound and ^{99m}Tc-sestamibi in our patients is shown in table 3.

Table 3. Sensitivity and specifisity of ultrasound and ^{99m}Tc-sestamibi in patients with secondary hyperparathyroidism and concomitant thyroid disease.

	S	SP
US	50%	80%
^{99m}Tc-sestamibi	45%	85%

Ultrasound revealed thyroid pathology in all ten patients that were included in this study. ^{99m}Tc-sestamibi on the other hand demonstrated thyroid pathology only in 3 patients. Thus, based on the ultrasound findings, we could anticipate what the patient would require in the theatre and the operative findings were more predictable and expectable.

At follow up all patients were normo-calcaemic and euthyroid. Six of them were on thyroxin tablets. The level of iPTH was within normal limits in 7 patients. In the 2 patients with less than four parathyroid glands removed and in 1 with four glands removed and autotransplantation the iPTH was marginally elevated. All these 3 patients were treated medically and did not require any further surgical intervention.

Discussion

In primary hyperparathyroidism a single adenoma is usually found (80%) and very rarely is the result of primary hyperplasia [5]. The need for preoperative localization is not very clear. An experienced surgeon, dealing with endocrine surgery, is able to localize the diseased gland during the first operation in 95% without any pre-operative localization studies [2]. On the other hand, supporters of the pre-operative localization argue that the exact localization of the parathyroid glands will result in a limited neck exploration [6]. ^{99m}Tc-sestamibi and ultrasound can localize the gland and make the operation easier and safer. With the advent of minimally invasive parathyroidectomy preoperative localization becomes absolutely necessary [7]. Besides, in radioguided surgery, parathyroidectomy can be performed even under local anesthesia [8].

In secondary hyperparathyroidism histology will show hyperplasia in almost every case and the sensitivity of various studies for parathyroid localization ranges from 41-70% [9]. For the preoperative localization computed tomography, magnetic resonance imaging and in a wide extend ultrasound and ^{99m}Tc-sestamibi have been used. For the ^{99m}Tc-sestamibi scintigraphy three scanning methods are in use: a) single isotope dual-phase scan, b) dual-isotope subtraction scan and c) three-dimensional studies [3]. The second method is more sensitive but in the clinical practice the first one is more frequently used. In hyperplasia the sestamibi washout is faster than in adenoma and one should consider either to obtain the delayed images earlier (at 2 hrs) or to adopt the dual-isotope subtraction scan as the routine investigation for every patient suffering from secondary hyperparathyroidism. This of course will increase the treatment cost.

With both, ^{99m}Tc-sestamibi and ultrasound scan, localization of parathyroid glands grossly correlates with the weight and the size of the glands. In our study the glands identified with ^{99m}Tc-sestamibi presented a higher mean weight compared to those not identified ($p<0.05$), while with ultrasound the difference was not statistically significant ($p=0.21$). In ^{99m}Tc-sestamibi scintigraphy, the radionuclide uptake depends on the gland activity as well [10]. Thus in secondary hyperparathyroidism, localization of parathyroid does not simply demonstrate enlarged glands but hyperfunctioning as well, that is a gland with tertiary hyperparathyroidism [11]. If we consider the findings from patients 1 and 3 (diffuse hyperplasia, none parathyroid localized) then one can speculate that in the glands not demonstrated with ^{99m}Tc-sestamibi either the disease has not progressed from diffuse to nodular hyperplasia [12] or from secondary to tertiary hyperparathyroidism.

The sensitivity of ^{99m}Tc-sestamibi in secondary hyperparathyroidism in various studies ranges from 44 to 55% [13]. In one of our studies we found a sensitivity of 49% [14]. This sensitivity can be significantly improved with dual-isotope subtraction scan with ^{99m}Tc-sestamibi/iodine-123 [15].

The sensitivity of ultrasound scan ranges from 43 to 70% [16]. It depends on the size of the diseased gland. Ultrasound can also detect superimposed thyroid disease. It is a cheap method, lasts a few minutes and is available in every hospital.

Coexistent thyroid disease in patients with secondary hyperparathyroidism is not rare (14% in our study). A connection between the two pathologies does not seem to exist. The combination of nodular goiter and hyperparathyroidism may be coincidental and can be partially explained by the high prevalence of these two conditions in middle aged women coming from mountainous areas [17]. In patients with secondary hyperparathyroidism and concomitant multinodular goiter, especially a toxic one, a significant number of false positive results is expected. This is because the radionuclide will be uptaken by the hyperfunctioning thyroid nodule [18]. Besides, this may happen even in the presence of cold thyroid nodules since enhanced or normal ^{99m}Tc-sestamibi uptake in more than 50% of these nodules has been reported [19].

Ultrasound scan can also give false positive results in patients with secondary hyperparathyroidism and concomitant thyroid disease. In 2 of our patients the ultrasonographer estimated the size of the parathyroid glands. Their size however was significantly different after surgical removal ($p<0.05$). So, one could argue that what was considered as a parathyroid preoperatively, most probably represented a thyroid nodule.

Patients with secondary hyperparathyroidism because of chronic renal failure require bilateral neck exploration, total parathyroidectomy and autotransplantation. ^{99m}Tc-sestamibi and ultrasound scan, whether they are used jointly or alone, present low sensitivity in preoperative localization and this may become lower in case of superimposed thyroid disease. One cannot but question the necessity of pre-operative localization studies in patients undergoing first neck exploration. The only advantage would be the localization of either ectopic or supernumerary glands. Their frequency however is very low [20] and so the majority of the patients are having a study that is not very helpful to an experienced surgeon. Besides, even if a gland is localized preoperatively with either ^{99m}Tc-sestamibi or ultrasound, one still needs to find it during the operation and remove it surgically. The presence of thyroid nodules will make this task harder, highlighting even more the importance of an experienced surgeon.

In our patients the sensitivity of ^{99m}Tc-sestamibi and ultrasound (45% and 50% respectively) (Table 3) was found to be within the limits reported in the literature. Only 10 glands (26.3%) however, were identified by both studies. Some of the other 28 glands could very well be thyroid nodules. This is most probably the case in patient's 5 left upper and left lower parathyroid glands.

In case of recurrent or persistent disease caused by supernumerary, ectopic or not found gland and in patients with a history of neck exploration, the ultrasound scan is of no use. In these cases subtraction scan with ^{99m}Tc/ ^{99m}Tc-sestamibi or ^{99m}Tc/iodine-123 is absolutely necessary for the pre-operative localization of diseased glands [21].

Ultrasound scan could be requested in every patient with secondary hyperparathyroidism who is going to undergo parathyroidectomy for a first time. In this way, we could identify those with concomitant thyroid disease and either proceed to parathyroidectomy or request further investigations. The cost advantage of preoperative localization could be improved by firstly performing ultrasound and secondly restricting ^{99m}Tc-sestamibi for cases in which ultrasound is non-diagnostic and for recurrences [22]. The relatively poor imaging results in patients with secondary hyperparathyroidism and concomitant thyroid disease, combined with the a priori need for bilateral exploration, makes routine preoperative imaging less attractive in these patients unless one is dealing with a re-operative situation.

ΠΕΡΙΛΗΨΗ

Ν Σύκας, Δ Γάκης, Δ Τακούδας, Γ Βέργουλας, Ι Φούζας, Ν Καρατζάς, Α Αντωνιάδης. **Προεγχειρητική εντόπιση των παραθυροειδών αδένων σε ασθενείς με δευτεροπαθή υπερπαραθυρεοειδισμό και συνυπάρχουσα θυρεοειδική νόσο.** Ιπποκράτεια 2000, 4, 1: 19-25

Το ^{99m}Tc-sestamibi και το υπερηχογράφημα του τραχήλου είναι οι πιο συχνά χρησιμοποιούμενες απεικονιστικές μέθοδοι για την προεγχει-

ρητική εντόπιση των παραθυρεοειδών αδένων σε ασθενείς με δευτεροπαθή υπερπαραθυρεοειδισμό. Ο σκοπός αυτής της μελέτης είναι η εκτίμηση της αξίας και της χρησιμότητας της προεγχειρητικής εντόπισης των παραθυρεοειδών σε ασθενείς με συνυπάρχουσα νόσο του θυρεοειδούς και δευτεροπαθή υπερπαραθυρεοειδισμό.

Στο διάστημα 1996-98 διενεργήθηκαν στο κέντρο μας 72 παραθυρεοειδεκτομές σε ασθενείς με δευτεροπαθή υπερπαραθυρεοειδισμό. Σε 10 ασθενείς συνυπήρχε θυρεοειδική νόσος (14%). Για την προεγχειρητική εντόπιση των αδένων χρησιμοποιήθηκε το υπερηχογράφημα και το σπινθηρογράφημα των παραθυρεοειδών με ^{99m}Tc-sestamibi.

Με το υπερηχογράφημα απεικονίσθηκαν 19 παραθυρεοειδείς αδένες από τους 38 που ανευρέθησαν χειρουργικά (50%). Το μέσο βάρος τους ήταν 0.738 gr vs. 0.438 gr αυτών που δεν απεικονίσθηκαν και το μέσο μέγεθός τους ήταν 1.221 cm vs. 0.973 cm (p=0.21). Με το ^{99m}Tc-sestamibi απεικονίσθηκαν 17 αδένες (45%) με μέσο βάρος 0.836 gr vs. 0.387 gr αυτών που δεν απεικονίσθηκαν ($p<0.05$) και μέσο μέγεθος 1.294 cm vs. 0.938 cm ($p<0.05$). Δύο αδένες δεν ανευρέθησαν. Μόνο 10 παραθυρεοειδείς (26.3%) εντοπίσθηκαν από αμφότερες τις μεθόδους (μέσο μέγεθος 1.38 cm και μέσο βάρος 0.991 gr). Το υπερηχογράφημα απεικόνισε την συνυπάρχουσα παθολογία του θυρεοειδούς και στους 10 ασθενείς (100%) ενώ το ^{99m}Tc-sestamibi μόνο σε 3 (33%). Η ιστολογική εικόνα των παραθυρεοειδών που ανιχνεύθηκαν με το ^{99m}Tc-sestamibi ήταν στην πλειονότητα των περιπτώσεων οζώδης υπερπλασία. Η συχνότερη ιστολογική εικόνα των θυρεοειδών ήταν πολυοζώδης βρογχοκήλη.

Αμφότερες οι απεικονιστικές εξετάσεις όταν χρησιμοποιούνται μεμονωμένα έχουν χαμηλή ευαισθησία (45% το ^{99m}Tc-sestamibi και 50% το υπερηχογράφημα) στην ανίχνευση των παραθυρεοειδών αδένων σε ασθενείς με δευτεροπαθή υπερπαραθυρεοειδισμό και συνυπάρχουσα παθολογία του θυρεοειδούς. Το υπερηχογράφημα μπορεί να δώσει πληροφορίες για τη θυρεοειδική νόσο και πρέπει να είναι η πρώτη και ίσως η μόνη μέθοδος που πρέπει να χρησιμοποιηθεί στους ασθενείς με δευτεροπαθή υπερπαραθυρεοειδισμό που πρόκειται να υποβληθούν για πρώτη φορά σε παραθυρεοειδεκτομή.

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