PRIMARY HYPERPARATHYROIDISM - STRATEGY FOR MULTIGLAND DISEASE IN THE ERA OF SPECT-CT

I.T. Cvasciuc*, W. Ismail, M. Lansdown

Leeds Teaching Hospitals, Department of Endocrine Surgery, Leeds, United Kingdom

Abstract

Purpose. To re-examine our clinical practice and review strategy for treatment of primary hyperparathyroidism in patients with multigland disease.

Methods. Retrospective analysis of 121 consecutive primary hyperparathyroidism (PHPT) patients who underwent surgery in a tertiary center between January 2010 and December 2014.

Results. Of 121 patients with PHPT 87% had single gland adenoma (SGD) and 13% had multigland disease (MGD). The overall cure rate was 95.86%. MGD was more frequent in younger persons (<40y)(50% vs. 13.2%). All patients had SPECT-CT (Single Photon Emission Computerized Tomography) with 28% being SPECT-CT negative. Patients with MGD had a higher rate of persistent disease (13.33% vs. 2.83%). Specimen weight was <600mg in 75% of MGD patients. 67% of SPECT-CT negative patients had mild hypercalcemia (Calcium <2.75 mmol/L) which was more frequent in MGD patients (43% vs. 19%).

Conclusions. MGD patients were more likely SPECT-CT negative (40% vs. 25.4%) and benefit from bilateral neck exploration (BNE) (74%). However, most SPECT-CT negative patients still have a single adenoma. In our series MGD was more frequent in younger patients, more likely SPECT-CT negative, often associated with mild hypercalcemia and had a higher persistence rate than SGD. BNE is the operation of choice in young, SPECT-CT negative patients. If ultrasound parathyroids suggests a single large adenoma, minimally invasive parathyroidectomy with intraoperative PTH monitoring can be considered.

Key words: multigland disease, hyperparathyroidism, SPECT-CT.

INTRODUCTION

Multigland gland disease (MGD), hyperplasia or multiple adenoma DA is responsible for 10-15% of primary hyperparathyroidism (PHPT). Patients with multigland disease have a marked heterogeneity in gland size and the cure rate is a little lower than for single gland

disease (SGD). Multiple preoperative scoring systems have been described in order to predict MGD. The preoperative scoring system described by Kebebew raises a high suspicion for MGD when <3 (1). The composite multi-gland disease scoring system (4D-CT imaging findings and biochemistry -serum calcium, PTH, the product of serum calcium and PTH) can identify patients with the likelihood of multi-gland disease (2, 3)(Table 1).

Chen *et al.* developed a mathematical model for intra-operative predictability of MGD (4). In our own practice in recent years we have routinely used MIBI (^{99m}Tc Sestamibi) SPECT-CT (3-dimensional single photon emission computed tomography), our preferred modality of parathyroid scintigraphy (5, 6) as an aid to determine which patients may have MGD and in planning surgery for patients with SGD. SPECT-CT provides fused functional and anatomical images with outcome depending on size/weight of gland and changes in serum Ca, PTH, serum vitamin D levels (7). MIBI SPECT-CT image fusion is superior to CT (computed tomography) or MIBI-SPECT alone and helps to predict MGD (8). SPECT-CT also helps to identify parathyroid adenomas overlying thyroid tissue, those located in the mediastinum and to differentiate parathyroid glands from lymph nodes and thyroid nodules, which can be challenging when performing ultrasound (US). Advantages of SPECT-CT are: better localization, lateralization and improved diagnostic performance (sensitivity 70–97%, specificity 83–100%)(9). Barczyński *et al.* are suggesting that negative imaging studies are highly predictive of MGD (10)(Table 2).

Non-localizing Sestamibi scans are more common in primary hyperparathyroidism with MGD and are associated with smaller-volume abnormal glands found at operation, with MGD being a potential cause of unsuccessful surgery (11, 8). Koberstein *et al.* concluded that SPECT-CT has a better accuracy for patients with higher PTH levels (12). Recurrence and persistent PHPT are more frequent in patients with MGD (13).

*Correspondence to: Ioan Titus Cvasciuc MD, Leeds Teaching Hospitals, Endocrine Surgery, Beckett Street, Leeds, LS101PJ, United Kingdom of Great Britain and Northern Ireland, E-mail: tituscvasciuc@gmail.com

Table 1

Characteristics of MGD (multigland disease)
Same incidence of MGD in young and old patients (14)
MGD patients should have genetic testing at any age (15)
MGD are more likely to have lower gland weight (16)
Lower Wisconsin Index score, small size(<7 mm), likelihood of having zero or multiple lesions on 4D-CT (1)
Higher intraoperative failure rate when using ioPTH measuring (15) and slower decline of ioPTH(>75% criteria to be used) (17)
Mild hyperparathyroidism is more frequent in MGD patients (16)
SPECT-CT has a better sensitivity than US, planar protocol and is equal with MET PET CT (see below)

MATERIAL AND METHODS

Retrospective analysis of 121 consecutive PHPT patients who underwent surgery in a tertiary center was carried out, between January 2010 and December 2014 (known multiple endocrine neoplasia MEN, familial, secondary, tertiary hyperparathyroidism, parathyroid carcinoma, or lithium induced disease were excluded). IoPTH (intra-operative PTH measuring) was not used routinely. All patients with confirmed biochemical disease had preoperative SPECT-CT and US (ultrasound) of parathyroid glands. Surgical and pathology reports were used to confirm type of operation, numbers, weights and microscopic report (adenoma/hyperplasia).

Biochemical cure was defined as a normal

Table 2. Sensitivity and specificity for different imaging techniques in primary hyperparathyroidism

	Sensitivity	Specificity
SPECT-CT (11)	47%	
SPECT-CT (16)	63.3%	
US parathyroid (16)	36.4%	
SPECT-CT (18)	30%	
MET PET CT (18)	30%	
SPECT-CT (11)	70%	83%
Planar protocol (19)	62%	75%
SPECT-CT (19)	77.5%	96.77%
SPECT (19)	67.34%	87.09%

calcium level at 6 months.

Technique: GE NM/CT 690 pro with 16 slice diagnostic quality CT; ^{99m}Tc labelled MIBI (Adult 900MBq) slow intravenous (IV) injection. Acquisition using Hi Res Collimator; Planar images: 10 min post injection 128 x 128 300 - 600s no zoom, 90 min post injection 128 x 128 300 - 600s no zoom with SPECT/CT at 90 mins. The results were analysed using SPSS software (2007).

RESULTS

Thirty-three of the 121 patients (28%) were SPECT-CT negative. In 106 patients (87%) we found a single functional adenoma and MGD in the other 15 patients (13%)(Fig. 1).

Figure 1. Fusion Sestamibi/CT parathyroids (left inferior gland and “brown fat” uptake in supraclavicular fossa).

Figure 2. A: Heterogeneity in size and shape of parathyroid glands in MGD; B: Similar picture in another patient.

Patients with MGD were more likely to be SPECT-CT negative (6/15 patients - 40%) than patients with single gland disease (27/106.25%, $p = 0.09$). Patients with a negative imaging study had a higher likelihood of MGD (9/15, 60%) than patients with a probable adenoma 9/88 (10%, $p = 0.08$). SPECT-CT was less sensitive for MGD than SGD (46.67% vs. 91%). Specificity of SPECT-CT was 75% for MGD and 50% for SGD.

Mild hypercalcemia (<2.75 mmol/L, <11 mg/dL) was more common in MGD patients (43%) than in patients with a single gland adenoma (19%, $p=0.04$) with mean serum calcium level of 2.72 mmol/L, 10.9 mg/dL) for SPECT-CT negative patients. Almost half of the MGD patients were under 40 years of age (7/15, 46.67%) at diagnosis while only 14/106 (13.2%) SGD patients were at young age at time of surgery ($p = 0.04$). There was no significant difference between distribution of MGD vs. SGD according to gender. Amongst -9

(7.43%) patients with discordant US and SPECT-CT studies, only $n=1$ (11.1%) had MGD. Bilateral neck exploration (BNE) was performed in 11 of the 15 patients with MGD (73.34%), the other 4 (26.67%) had minimally invasive parathyroidectomy (MIP). Patients with positive US and negative SPECT-CT were offered minimally invasive approach with ioPTH. In the MGD group patients eight had 2 parathyroid glands removed, 5 had 3 glands, and 2 had 4 lesions excised (Fig. 2). Mean weight of the glands was 560 mg for MGD and 980 mg for SGD specimens and decreased with increasing numbers of lesions (Table 3). Mean weight of specimens for SPECT-CT negative patients was 690 mg. $N=12$ (81.8%) of SPECT-CT negative patients had SGD. All these patients were offered BNE (Fig. 3).

The cure rate at 6 months was 95%. Five patients had persistent disease, 2 of the 15 with MGD (13.33%) and 3 of the 88 with SGD 2.83% ($p = 0.04$) (Table 4).

DISCUSSION

Our results suggest that SPECT-CT negative imaging helps predict MGD especially in patients, with mild hypercalcemia and/or under 40 years. As surgery

Figure 3. SPECT-CT parathyroids with right inferior enlarged parathyroid gland.

Table 3

	MGD patients	SGD patients
Number	15(12.4%)	106(87.6%)
Gender F:M	9:6	62:44
Age <40	7	14
Mild hypercalcemia	6 (43%)	20(19%)
SPECT-CT	6(43%)	27(25%)
Weight <600 mg	18/24	12/106
BNE	11(73.34%)	10(9.43%)
MIP	4(26.67%)	96(90.56%)
Cure rate	95%	97%

Table 4

Patient	SPECT - CT	USS	BNE
1	-ve	-ve	Yes
2	-ve	-ve	Yes
3	+ve	+ve	MIP
4	-ve	+ve	Yes
5	+ve	+ve	MIP

for MGD has a higher rate of failure, prediction prior to surgery is of great value as it helps select a group of patients likely to need longer time allocated for surgery and additional techniques such as ioPTH (15).

Some authors have used the CaPTHUS score to predict MGD. Patients with CaPTHUS>3 are more likely to have MGD disease and ioPTH has been recommended for these patients (20). There was no correlation for MGD with gender in our study, however some studies showed a male predominance in patients under 40 years (8). In our study sensitivity for SPECT-CT is significantly lower for MGD than for SGD (46.67% vs. 91%) which is similar to other recent published studies (21).

SPECT-CT and US are the most used modalities for parathyroid localization. MRI (magnetic resonance imaging) and CT (computed tomography) scan are an option but less frequent in use. 4DCT (four-dimensional computed tomography) and 11 C-methionine PET/CT (a hybrid technique) could be used (if available and other methods have failed) while keeping in mind radiation exposure to the thyroid gland (21, 22). Invasive studies (selective venous sampling and parathyroid arteriography) are mainly used for persistent and recurrent disease, in SPECT-CT negative patients (2, 23, 18). Weber *et al.* concluded that sensitivity for 11C-methionine PET/CT is 83% for SGD and 67% MGD (5). 4D-CT is an expensive technique recommended for older patients, for re-do operations and for SPECT-CT and US negative cases (17, 24, 25).

MGD is often associated with mild PHPT and a slower decline in ioPTH (26, 27). Patients with unsuccessful or discordant preoperative localization have a higher incidence of multigland disease and therefore lower cure rate (28). Discordance between thyroid lobe lengths on the early phase ^{99m}Tc Sestamibi

Figure 4. Algorithm for treatment of primary hyperparathyroidism used at Leeds Teaching Hospitals.

scans compared with cervical ultrasonography has led to successful preoperative identification of parathyroid adenomas (29). Patients with recognized or suspected MGD should be offered ioPTH measuring with a final post excision decrease of PTH >75% from the baseline and/or PTH levels in the normal range (14).

Despite availability of cinacalcet, surgery remains the treatment of choice for most patients with symptomatic PHPT with an expected cure rate of 95% (3). There is a small group of SPECT-CT negative patients in whom US demonstrates an apparently single adenoma who might be suitable for MIP with ioPTH guiding further surgery (30). For the remainder of image negative patients BNE is appropriate approach. If SPECT-CT suggests a single adenoma routine BNE is not necessary in younger individuals (31). Where available intraoperative MRI could be a useful tool for identification of enlarged parathyroids during surgery (32).

Is there any indication for gene testing prior to surgery? Yes, patients under 30 years and MGD patients at any age could benefit from genetic testing and should be checked for genetic mutation (MEN1 first and if negative for MEN 4, familial idiopathic primary hyperparathyroidism (FIPHT), hyperparathyroidism jaw tumour syndrome (HPT-JT), familial hypocalciuric hypocalcemia (FHH), autosomal dominant moderate hyperparathyroidism (ADMH) and neonatal severe hyperparathyroidism (NSHPT) (33, 10). Barczyński *et al.* (10) suggest that all patients with negative scans and with high likelihood of MGD to be referred to specialized centres for genetic testing (MGD disease patients under the age of 40) and parathyroid surgery. Our cure rate for MGD patients is according to recent data published in literature (European Society of Endocrine Surgeons ESES Workshop 2015, 10, 34) and is just slightly lower than the cure rate for surgery for SGD.

In conclusion, in our series MGD was more frequent in younger patients presenting with mild hypercalcemia. MGD patients had a higher risk of persistent disease and were more likely to be SPECT-CT negative. ^{99m}Tc-MIBI SPECT-CT sensitivity is significantly lower in MGD than in SGD. We believe patients with SPECT-CT negative scans should be offered surgery in a center with an experienced parathyroid team. We think we can improve our results with more liberal use of ioPTH especially in patients under 40 years. Communicating the suspicion for multigland disease in the radiology report could influence surgery.

Our suggested strategy. In biochemically proven PHPT we use SPECT-CT and US parathyroids to localize enlarged glands (US helps also to characterize thyroid nodules) (Fig. 4).

If both imaging studies are concordant and positive we suggest proceeding with MIP (ioPTH or frozen section if any uncertainty during operation and if age under 40 years). If both modalities of imaging are negative or inconclusive but we are confident of the biochemical diagnosis, we proceed to surgery with ioPTH measuring and frozen section in the traditional way (bilateral neck exploration).

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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