Bilateral neck exploration in patients with primary hyperparathyroidism and discordant imaging results: a single-centre study

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Abstract

Introduction: Focused parathyroidectomy is the treatment of choice for patients with concordant positive imaging. Bilateral cervical exploration is performed for cases with discordant imaging, yet more than 70% of those cases are the result of a single-gland disease. As focused parathyroidectomy is generally costless and harmless, for cases with discordant imaging, we tried to determine whether preoperative characteristics can lead to a diagnosis of single-gland disease.

Methods: This study included 182 patients treated for primary hyperparathyroidism by bilateral exploration from 2009 to 2012 at La Timone Hospital, Marseille, France. We classified patients based on preoperative images and pathological results (single-gland or multiglandular disease). We then compared the demographical, laboratory and imaging results. We also asked a senior nuclear medicine practitioner who was blind to the ultrasound and pathological results to perform a second reading.

Results: Of the total number of patients, 15.4% had negative, 54.4% discordant and 30.2% concordant imaging. After reviewing the scintigraphy results, 8% of the cases with discordant imaging would have been classified as concordant with ultrasound. Subtraction scintigraphy obtained better results than dual-phase scintigraphy (concordance with ultrasound in 50 vs 31% with classical scintigraphy). For the cases of discordant imaging, no predictive factors of single-gland disease could be identified. Ultrasound and scintigraphy were similarly effective in determining the correct location of the abnormal gland.

Conclusion: Discordant results of preoperative imaging modalities do not discriminate between uniglandular and multiglandular diseases in hyperparathyroidism. Diagnostic differentiation between the different causes of hyperparathyroidism requires improvements in imaging techniques and might benefit from subtraction scintigraphy.

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Introduction

Primary hyperparathyroidism (PHPT) is the first aetiology of hypercalcaemia and the third most frequently occurring endocrine disease. Its prevalence is estimated to be 0.1–2%, while its incidence has increased over recent years up to 30/100 000 per year. PHPT rarely leads to severe hypercalcaemia; it is now frequently diagnosed at an asymptomatic stage and less frequently because of

recurring kidney stones or osteoporosis. Thus, PHPT is, in the large majority of cases, a benign disease that is responsible for increased morbidity, and it requires an optimal and harmless management strategy (1, 2, 3).

PHPT is the result of a single adenoma in 80–85% cases. Initial imaging workouts, i.e. ultrasound and ^{99m}Tc-sestamibi scintigraphy, are aimed at determining

the uniglandular or multiglandular nature of the disease to allow focused parathyroidectomy (4, 5), the preferred treatment for cases of single adenoma. In contrast, multiglandular disease (adenoma or hyperplasia), which has been reported in 15–20% cases, requires bilateral exploration (1, 4, 5, 6). Imaging sensitivity depends on the nature of the disease: up to 91 vs 30–45% for scintigraphy (4, 7, 8, 9) and 77–80 vs 16–35% for ultrasound in single-gland vs multiglandular disease respectively (9, 10). In contrast, the specificity for both procedures is 91–98% (11, 12, 13). Moreover, the success of ultrasound mainly depends on the radiologist's experience (14). Data in the literature showed that up to 89% of cases of single adenoma could be individualised using both techniques (15). However, 24–27% of preoperative imaging results are discordant (6, 16) and 12–18% are negative (17, 18, 19); for these cases, the gold standard for surgery remains bilateral exploration (5). The choice between the treatment strategies of focused parathyroidectomy and bilateral exploration remains a matter of debate (20, 21, 22, 23). However, recent data in the literature suggested that focused parathyroidectomy was less expensive and induced fewer side effects with at least identical remission rates, resulting in a shorter hospital stay (5, 24). Increasing the number of patients treated by focused parathyroidectomy should be the main objective of pre-surgical imaging workouts.

We decided to focus on patients with PHPT with discordant imaging. As bilateral exploration has previously been used for all patients with negative or discordant imaging at our centre, we retrospectively evaluated all the patients with bilateral exploration between 2009 and 2012. Our main objective was to determine whether clinical, laboratory or preoperative imaging results could have guided the surgeon to the identification of a uniglandular disease resulting in a less invasive surgery, despite the presence of discordant or negative imaging.

Subjects and methods

All patients treated for PHPT by bilateral exploration in the Department of Endocrine Surgery of La Timone Hospital, Marseille, France, between May 2009 and June 2012 were retrieved from a local database. This selection criterion was justified by the systematic bilateral neck exploration in case of discordant or negative imaging (ultrasound and scintigraphy) in our department. We included only patients who had their initial imaging workout at our hospital, including ultrasound performed by a radiologist specialised in thyroid and parathyroid ultrasound

(J Vaillant) and a ^{99m}Tc -sestamibi scintigraphy performed by a senior nuclear medicine practitioner. All patients signed a consent allowing the retrospective study to be performed, as required by the Ethics Committee of our institution.

PHPT was defined by hypercalcaemia associated with a non-decreased parathormone (PTH) level. Blood samples were obtained and analysed systematically at the Department of Biology at La Timone Hospital. The laboratory normal values were: plasma calcium level, 2.25–2.58 mmol/l; phosphorus level, 0.79–1.53 mmol/l; PTH level, 15.1–65.1 pg/ml and vitamin D level, 75–250 nmol/l. Calcium level was corrected when albumin level was <38 g/l.

For each patient, demographic (sex and age at diagnosis), laboratory (plasma calcium, phosphorus, PTH, vitamin D, urea, creatinine and urinary calcium levels), genetic (*menin* (*MEN1*), *RET* and *HRPT2* (*CDC73*), when performed) and imaging results (ultrasound and scintigraphy) were recorded. Ultrasound and scintigraphy were considered to be concordant when the precise location (side and upper or lower position) and the exact number of glands considered abnormal were similar. Preoperative (number of glands resected) as well as post-surgical laboratory data (plasma calcium and PTH) were also recorded. The pathology data included the weight of the glands (mean in case of multiglandular disease) and the number and nature of the pathological gland(s) (adenoma or hyperplasia). The patient was considered to be cured when the post-operative plasma calcium level was low or normal and all four glands had been visualised during the surgery or when the intraoperative PTH level had decreased (>50%) in case of incomplete visualisation.

To better characterise this cohort, we first classified patients into three groups based on their imaging results: group 1 with positive concordant imaging (including one or several abnormal glands), group 2 with discordant imaging (with only one positive image or both positive but with different results) and group 3 with negative imaging. We then compared the demographic and laboratory characteristics and pathological findings in each group.

As a second step, we classified patients into two groups based on the uni- or multiglandular nature of their disease determined by the pathological findings. Parathyroid disease could be classified as adenoma or hyperplastic gland. Patients who were not cured after surgery despite a single pathological gland resection were finally classified as having multiglandular disease. We compared the demographic, laboratory and imaging characteristics between these two groups to determine whether some

Figure 1
Flow chart summarising the characteristics of patients included.

pre-surgical parameters could have guided the clinician to the diagnosis of a single-gland disease when the imaging results were discordant. In the uniglandular disease group with discordant preoperative imaging, we also compared the performance of ultrasound and scintigraphy (divided into two groups, dual-phase sestamibi vs iodine-123-technetium-99m-sestamibi subtraction scintigraphy) for defining the correct location of the pathological gland. Finally, we asked a second senior physician of the Department of Nuclear Medicine (D Taieb), specialised in endocrine disease and blind to the results of the ultrasound and the final pathological result, to read all the scintigraphies, which had been originally performed by a different nuclear medicine practitioner.

Statistics were performed with XLStat Software (Adinsoft, Paris, France). The quantitative data are presented as the means $\pm$ s.d. The qualitative data were compared by the χ^2 or Fisher's exact test. The quantitative data were compared by ANOVA or Student's *t*-test. A *P* value of <0.05 was considered significant.

Results

In this retrospective study, 182 patients, 131 females and 51 males (mean age at diagnosis: 62.8 ± 13.5 years), were included (Fig. 1). The demographic and laboratory pre- and post-surgical data are summarised in Table 1. The median follow-up was 0.3 month (min., 0.3 and max., 36). At last follow-up, 174 patients (95.6%) were cured. A total of eight patients were uncured. Their main characteristics are available in Supplementary Table 1, see section on supplementary data given at the end of this article.

Classification based on imaging results

A total of 55 patients (30.2%) had both positive and concordant ultrasound and scintigraphy imaging (group 1). Bilateral cervical exploration was justified because of the need for thyroid resection in 27 patients (49%), imaging showing several abnormal glands in 16 patients (29.1%), the mediastinal or ectopic location of the parathyroid gland in four patients (7.3%) or recurrence in eight patients (14.5%). Of the total number of patients, 99 (54.4%) had discordant imaging (group 2), and 28 patients (15.4%) had negative imaging for both ultrasound and scintigraphy (group 3) (Fig. 2).

Pre-surgical characteristics ► The demographic (age at diagnosis and sex ratio) and laboratory data (plasma calcium, PTH and vitamin D levels) were not significantly different among the three groups. Additionally, there was no significant difference in the number of bilateral explorations due to thyroid resection between the three groups ($P=0.66$).

The imaging workouts included 138 (76%) dual-phase sestamibi scintigraphies and 44 (24%) subtraction scintigraphies.

Patients with positive concordant imaging underwent subtraction scintigraphy (32.7% of cases) more frequently than patients with discordant or negative imaging (21.2 and 17.8% of cases respectively) ($P=0.02$). Concordance with the pathology results was more frequent with subtraction scintigraphy than with classical sestamibi scintigraphy (50 vs 31%, $P=0.02$). For patients with discordant imaging, there was no significant difference between scintigraphy and ultrasound in determining the

Table 1 Main characteristics of the whole population ($n=182$). Data are presented as mean $\pm$ s.d.

Characteristics	Values
Preoperative data	
Sex ratio (female:male)	131:51 (72%:28%)
Age at diagnosis (years)	62.8 ± 13.5
Calcium (mmol/l)	2.74 ± 0.2
Phosphorus (mmol/l)	0.82 ± 0.2
PTH (pg/ml)	168.3 ± 177.5
Vitamin D (nmol/l)	59.4 ± 33.6
Creatinine (μ mol/l)	74.9 ± 42.9
Postoperative data	
PTH D0 + 4 h (pg/ml)	20.3 ± 43.9
PTH D1 (pg/ml)	27.4 ± 48.3
PTH D8 (pg/ml)	49.5 ± 47.4
Calcium D1 (mmol/l)	2.21 ± 0.17
Calcium D8 (mmol/l)	2.27 ± 0.17
Follow-up (months)	3.03 ± 7.4

PTH, parathormone; D0, day of surgery; D1, first post-operative day; D8, eighth postoperative day.

Figure 2

Imaging characteristics of patients included.

correct location of the abnormal gland(s) (43.5 vs 38.5% respectively; $P=0.43$).

A second reading by a specialised nuclear medicine practitioner allowed 9% ($9/99$) of discordant scintigraphy cases to be classified as concordant with ultrasound. If a second reading had been performed before surgery, 8% of discordant scintigraphy cases would have been considered as positive concordant imaging in favour of single-gland disease, leading to focused parathyroidectomy.

Pathology ► There was no significant difference in the rate of multiglandular disease among the three groups (29 , 30.5 and 28% in groups 1, 2 and 3 respectively; $P=0.717$). The mean gland weight was significantly lower in patients with negative imaging for both ultrasound and scintigraphy when compared with patients with concordant positive imaging (0.39 ± 0.32 vs 1.22 ± 1.13 g; $P=0.04$). There was no significant difference when comparing patients with negative or positive imaging and those with discordant imaging (mean weight: 0.984 ± 1.03 g; Table 2).

Post-surgical data ► The remission rates were similar among the three groups (94.5 , 94.1 and 96.4% for groups 1, 2 and 3 respectively; $P=0.98$). The mean follow-up was

not significantly different between the three groups (0.83 ± 2.75 , 3.99 ± 8.45 and 3.99 ± 8.16 months, for groups 1, 2 and 3 respectively; $P=0.138$).

Classification based on single-gland vs multiglandular disease

Pathological results of resected glands were normal for nine patients (4.9%). Of the 173 remaining patients, 122 (70.5%) had a single-gland disease, whereas 51 (29.5%) had a multiglandular disease. In the single-gland disease group, the pathological analysis revealed an adenoma in 83% and a hyperplasia in 17% of cases. In the multiglandular disease group, 55.5% had two abnormal glands, 28.9% had three abnormal glands and 15.5% had four abnormal glands.

Post-surgical data ► The gland weight was not significantly different between the two groups (single-gland vs multiglandular disease; $P=0.08$). Patients with multiglandular disease more frequently had a calcium level <2.2 mmol/l (37.5 vs 19.2% ; $P=0.018$) at day 8. All the uncured patients ($n=8$) presented with multiglandular disease.

Pre-surgical predictive factors of single-gland disease ► We tried to determine retrospectively whether some preoperative predictive factors could have guided the surgeon to the diagnosis of a single-gland disease in case of discordant imaging.

There was no significant difference in terms of demographic (age at diagnosis and sex) or laboratory data, including plasma calcium, phosphorus and creatinine levels, between the two groups. In the univariate analysis, the pre-surgical PTH level was significantly higher in the multiglandular vs the single-gland disease groups (mean: 220 ± 238 vs 152 ± 143.5 pg/ml; $P=0.02$). However, the vitamin D level was also significantly

Table 2 Main preoperative and pathological results for the three imaging groups of patients.

	Patients with concordant imaging	Patients with discordant imaging	Patients with negative imaging	P
Calcium (mmol/l) (mean $\pm$ s.d.)	2.75 (± 0.25)	2.73 (± 0.17)	2.72 (± 0.14)	0.57
PTH preoperative level (pg/ml) (mean $\pm$ s.d.)	201 (± 266)	152 (± 142)	126 (± 124.1)	0.47
Thyroid pathology (patients)	27/55 (49%)*	30/99 (30.3%)	5/28 (17.8%)	0.04
Weight of pathological gland (g) (mean $\pm$ s.d.)	1.22 (± 1.13)*	0.984 (± 1.03)	0.39 (± 0.32)*	0.04*
Uniglandular disease (patients)	39/55 (71%)	69/99 (69.5%)	20/28 (72%)	0.72
Multiglandular disease (patients)	16/55 (29%)	30/99 (30.5%)	8/28 (28%)	0.72

Significant result (* $P<0.05$) between these two groups of patients.

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Table 3 Comparative characteristics of patients with single-gland vs multiglandular disease. Data are presented as mean $\pm$ s.d.

	Patients with single gland disease	Patients with multiglandular disease	P
Age at diagnosis (years)	63.88 $\pm$ 13	61.93 $\pm$ 14.1	0.38
Calcium level (mmol/l)	2.75 $\pm$ 0.19	2.75 $\pm$ 0.22	0.94
PTH (pg/ml)	151.97 $\pm$ 143.53	219.75 $\pm$ 238.01	0.02
Vitamin D (nmol/l)	64.01 $\pm$ 36.86	49.60 $\pm$ 24.14	0.01
PTH level at D0 + 4 h (pg/ml)	13.65 $\pm$ 9.59	30.57 $\pm$ 75.6	0.02
PTH level at D1 (pg/ml)	20.36 $\pm$ 14.98	38.94 $\pm$ 83.77	0.02
PTH level at D8 (pg/ml)	42.61 $\pm$ 22.38	64 $\pm$ 77.29	0.01

$P < 0.05$ was considered significant. PTH, parathormone; D0, day of surgery; D1, first postoperative day; D8, eighth postoperative day.

different between the two groups (mean: 50 ± 24.1 vs 64 ± 36.8 nmol/l; $P = 0.01$; Table 3).

The imaging results were better in cases of uniglandular disease: 47% of ultrasound results and 44.4% of scintigraphy results were concordant with the pathological findings in the single-gland disease group compared with only 14% in the multiglandular disease group ($P < 0.0001$).

Discussion

Our results showed a similar proportion of multiglandular disease in both negative and discordant imaging: multiglandular disease was observed in 28–30% of patients, which means that 70% of the cohort had a single-gland disease. Surprisingly, the rate of multiglandular disease was not significantly different among these two groups and the group of patients with concordant positive imaging. However, this latter group was biased by the inclusion of patients with several concordant images and the exclusion of patients treated by focused parathyroidectomy because of a single positive and concordant image ($n = 590$ in the same period). Thus, our data do not contradict previously published data, which showed that multiglandular disease was more frequent in case of discordant or negative imaging (19, 25, 26).

We did not identify pre-surgical factors of single-gland disease other than imaging. The only significant parameter was the level of PTH, which was higher in the multiglandular disease group. However, this was probably explained by lower levels of vitamin D. Discordant results have been reported in the literature: Thakur *et al.* (27) did not show any difference in PTH or calcium levels in cases of single-gland and multiglandular diseases. In contrast, Kebebew *et al.* (26) created a score that included calcium, PTH and imaging results allowing for the detection of uniglandular disease with a 100% positive predictive value and specificity. On one hand, using this score for our

patients with discordant imaging would have led to a false conclusion of single-gland disease in 26.7% of cases; on the other hand, it would have clearly increased the numbers of appropriate surgical approaches, i.e. the rate of focused parathyroidectomy in case of single-gland disease. The difference in the predictive value of this score in our study could be explained by our selection criteria; we used this score to assess a more challenging population, which theoretically represents only one-fourth of all patients with hyperparathyroidism.

When imaging was discordant, none of the imaging was superior in localising the abnormal gland, in contrast with previous literature data (25, 28). Our results suggest that the use of systematic subtraction scintigraphy and a second reading by a specialised nuclear medicine practitioner added to the pre-surgical score would clearly increase the rate of focused parathyroidectomy in patients with discordant imaging. However, literature data showed discordant results, with a better sensitivity, but a lower predictive positive value for subtraction vs classical scintigraphy (11, 29). This point is difficult to consider in our patients due to the initial selection bias in our cohort. A second reading of the scintigraphy by a specialised nuclear medicine practitioner increased the rate of concordant positive imaging with ultrasound (9% increase). This had already been shown for ultrasound; a second ultrasound imaging reading allowed 65% of discordant imaging results to be reclassified as concordant (16). Of note, the facts that ultrasound was performed by a specialised radiologist and that we included only the scintigraphies read by a senior physician of the Department of Nuclear Medicine probably explain why the rates of discordant imaging were lower than those in the literature (6).

Finally, performance of two preoperative imaging procedures (ultrasound and scintigraphy) remains theoretically debatable when the imaging is performed under optimal conditions and intraoperative PTH assay is

easily available (30): for instance, Kunstman *et al.* (5) recommended focused parathyroidectomy when the first imaging was clearly considered positive. In our patients with only one positive and formal imaging, the application of this management approach would have led to appropriate focused parathyroidectomy in 43% of our patients (and surgical conversion in enlarged cervicotomy in 57%; data not shown).

Our study has several limitations. As our main objective was to understand how to improve the management of patients with discordant imaging, we did not analyse the data of the 590 patients, with PHPT and concordant imaging, who underwent focused parathyroidectomy in the same period of time. The main advantage of our selection was that we had two subgroups of control patients: positive concordant with several images and negative concordant (i.e. negative imaging for both ultrasound and scintigraphy). The originality of this approach, however, makes it difficult to compare with previously published results, which included a majority of 'obvious' cases. Another limitation was the time between surgery and the determination of the calcium level used to define remission (8 days). As to whether or not this could hinder the identification of recurrence in patients who underwent focused parathyroidectomy, we believe that patients with bilateral exploration are less at risk of developing recurrence, as all of their glands would theoretically be explored, or as they would have had preoperative PTH samplings (data not shown). Finally, we tried to be as strict as possible in the definition of concordance. We considered images to be concordant only if they showed the same side and upper/lower location of the abnormal gland(s), while the majority of previously published studies used only the side of the gland in their definition of concordance. This strict criterion was used to ensure that only patients with absolute imaging certitude of a single-gland disease would be considered appropriate for focused parathyroidectomy.

To conclude, discordant or negative imaging does not necessarily mean multiglandular disease, as 70% of our patients had uniglandular disease. Therefore, these patients would clearly benefit from focused parathyroidectomy. Our study did not manage to identify any predictive factors other than imaging that could help distinguish between single-gland and multiglandular diseases. The only ways to improve the pre-surgical workout are based on a second reading by an expert nuclear medicine practitioner and the systematic use of subtraction scintigraphy. Taking into account the higher cost and morbidity of bilateral exploration, we believe that

our results emphasise the need for the management of PHPT in specialised centres including expert radiologists and nuclear medicine practitioners.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-13-0796>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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