Clinical role of $^{99m}TcO_4$/MIBI scan, ultrasound and intra-operative gamma probe in the performance of unilateral and minimally invasive surgery in primary hyperparathyroidism

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Received 17 March and in revised form 24 April 2001 / Published online: 5 July 2001

Abstract. The main purposes of this study were: (a) to investigate the efficacy of an imaging protocol based on the combination of $^{99m}TcO_4$/MIBI scintigraphy and neck ultrasound (US) in selecting patients with primary hyperparathyroidism (HPT) for unilateral neck exploration, and (b) to help define the role of the intraoperative MIBI gamma probe (IMGP) technique in the performance of minimally invasive radio-guided surgery (MIRS). One hundred and forty-three consecutive patients with primary HPT were enrolled in the study. We used a modified $^{99m}TcO_4$/MIBI scintigraphic procedure which included the oral administration of potassium perchlorate to cause rapid $^{99m}TcO_4$ washout from the thyroid tissue, thereby permitting the acquisition of high-quality early MIBI images. A single-photon emission tomography (SPET) acquisition was also obtained in 21 patients, of whom seven had an enlarged parathyroid gland (EPG) in the mediastinum at planar scintigraphy and 14 had discordant scan/US findings for the presence of a cervical EPG. Neck US was performed in the same session as scintigraphy using a small-parts, high-resolution 10-MHz transducer. All patients were then operated on by the same surgical team. Quick PTH assay (QPTH) was used to measure PTH intraoperatively to confirm successful parathyroidectomy. In patients with scan/US evidence of a solitary EPG and with a normal thyroid gland, limited, unilateral neck surgery or, more recently, MIRS was planned (*n*=91). In patients with scan/US evidence of multiglandular disease (MGD) (*n*=21) or concomitant nodular goitre (*n*=24) or in patients with a negative scan/US evaluation (*n*=7), extensive bilateral neck exploration was planned (*n*=52). In 87 of the 91 patients (95.6%) in whom preoperative imaging indicated the presence of a solitary EPG and a normal thyroid gland, a single parathyroid adenoma was found at surgery, and these patients were treated by unilateral neck exploration or MIRS. In the remaining four patients of this group, conversion to bilateral neck exploration was required because parathyroid carcinoma (*n*=3) or MGD (*n*=1) was diagnosed at operation. In some cases SPET was helpful in better localising the EPG. In particular, in 5 of the 21 patients evaluated, SPET localised an EPG deep in the neck or mediastinum and at surgery a parathyroid adenoma was found in the paratracheal or para-oesophageal space. In 43 of the 46 patients (93.5%) who were candidates for MIRS, the IMGP technique allowed parathyroidectomy to be performed through a small, 2- to 2.5-cm skin incision with a short duration of intervention (mean 34 min). We conclude that: (a) The integrated scan/US imaging protocol that we used appears to be accurate in selecting patients with primary HPT for unilateral neck exploration. (b) In our series the most prevalent cause of bilateral neck exploration was the co-existence of a nodular goitre; thus accurate preoperative evaluation of the thyroid gland by dual-tracer scintigraphy and US imaging is strongly recommended in all patients with HPT. (c) SPET can provide the surgeon with useful information when an EPG is located deep in the neck or mediastinum. (d) IMGP appears to be a useful intraoperative device in HPT patients with solitary parathyroid adenomas and a normal thyroid gland, since it permits minimally invasive and time-saving surgery.

Keywords: Primary hyperparathyroidism – $^{99m}TcO_4$/MIBI scintigraphy – High-resolution neck ultrasound – Intraoperative gamma probe – Minimally invasive radio-guided surgery

Eur J Nucl Med (2001) 28:1351–1359
DOI 10.1007/s002590100564

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Introduction

Despite the fact that primary hyperparathyroidism (HPT) is caused by a solitary adenoma in the majority of cases (approximately 85%) [1], many surgeons routinely use a bilateral neck exploration with the aim of identifying and even biopsying each parathyroid gland other than the adenoma, in order to investigate the possibility of multiglandular disease (MGD) [2, 3, 4, 5]. In contrast, other authors have reported that scintigraphy, alone or in combination with neck ultrasound (US), is able to accurately predict which patients with primary HPT may be adequately explored by means of a unilateral approach [6, 7, 8, 9]. The unilateral approach is also strongly favoured by the availability of intraoperative quick parathormone (QPTH) measurement: a prompt decrease in QPTH levels after removal of the enlarged parathyroid gland (EPG) represents a sensitive indicator of successful parathyroidectomy [10]. Furthermore, an even less invasive surgical approach has recently been proposed for primary HPT patients: this approach is based on intraoperative detection of the EPG by means of insertion of a gamma probe through a small skin incision, so-called minimally invasive radio-guided surgery (MIRS) [11]. In this paper, which follows publications documenting our preliminary findings [12, 13], we report further data obtained in a large group of 143 consecutive patients with primary HPT. The main aims of this study were: (a) to evaluate the role of a single-day imaging protocol based on the combination of $^{99m}TcO_4$/MIBI scintigraphy and high-resolution neck US in selecting patients with primary HPT as potential candidates for a limited neck exploration, (b) to investigate the usefulness of the intraoperative MIBI gamma probe (IMGP) technique in the performance of MIRS. The potential utility of single-photon emission tomography (SPET) imaging following planar scintigraphy was also examined.

Materials and methods

From September 1998 to June 2000, 143 consecutive patients with primary HPT were operated on at the general surgery department of Padova Hospital. Diagnosis of primary HPT was made on the basis of clinical and biochemical findings. There were 84 females and 59 males, aged 23–76 years (mean 47.3 years). Four patients had previously undergone partial thyroidectomy for a nodular goitre; 15 other patients had previously undergone unsuccessful parathyroid surgery in other hospitals. Four patients were affected by MEN syndrome, and two by familial HPT. When referred to our centre, all patients were investigated preoperatively by means of a single-day thyroid/parathyroid imaging protocol that included dual-tracer subtraction scintigraphy and high-resolution neck US, as previously described [12].

Preoperative imaging procedures. The scintigraphic procedure we used [12] consisted of the following steps (a–e = acquisition, f–h = processing): (a) $^{99m}TcO_4$ (150 MBq) was injected intravenously, (b) 20 min later, potassium perchlorate ($KClO_4$) (400 mg) was administered orally, (c) immediately after this, the patient's neck was immobilised under the gamma camera and a 5-min $^{99m}TcO_4$ thyroid scan was acquired, (d) MIBI (500 MBq) was injected intravenously, followed by a flush of saline (30 ml) to avoid venous tracer stagnation, (e) dynamic acquisition of seven MIBI frames, each lasting 5 min, was obtained, (f) background activity was subtracted from the $^{99m}TcO_4$ and MIBI frames, (g) MIBI images were normalised to the maximum pixel count activity of the $^{99m}TcO_4$ scan, (h) the $^{99m}TcO_4$ scan was subtracted from the MIBI images. The interpretative criteria for scintigraphy, in the absence of a nodular goitre, were as follows: (1) a scan showing a single focus of MIBI uptake was considered indicative of a solitary parathyroid adenoma, (2) a scan showing two or more foci of MIBI uptake was considered to be indicative of MGD. In patients with concomitant nodular goitre, the $^{99m}TcO_4$ scan and neck US were used to differentiate EPG(s) from thyroid nodule(s). The $KClO_4$ was administered with the aim of inducing $^{99m}TcO_4$ thyroid washout. In a previous investigation [12] performed on five euthyroid and US-normal subjects only injected with $^{99m}TcO_4$ (150 MBq), we noted that $KClO_4$ (400 mg given orally) was able to induce a rapid and significant decrease in thyroid activity (average decrease of 78% over 40 min). On the basis of these findings, we devised the $^{99m}TcO_4$ and $KClO_4$/MIBI procedure used in the present study. This scintigraphic technique allows us to obtain high-quality early MIBI scans with clear delineation of EPGs even if they are located behind the thyroid gland (an example is shown in Fig. 1). Another interesting aspect of this scintigraphic method is that, following the oral administration of $KClO_4$, there is a 10-min latency interval before the thyroid $^{99m}TcO_4$ washout begins; this time is sufficient to allow positioning of the patient under the gamma camera and acquisition of a $^{99m}TcO_4$ thyroid scan; subsequently, MIBI can be injected without moving the patient.

For scintigraphic examinations, a large-field-of-view (LFOV) gamma camera (Orbiter 7,500, Siemens, Hoffman Estates, Ill.) equipped with a parallel-hole low-energy, high-resolution collimator was used. Images were stored in a 128×128 matrix and processed using a dedicated computer (ICON workstation; Siemens, Hoffman Estates, Ill.).

In some patients with a $^{99m}TcO_4$/MIBI scan revealing an ectopic EGP focus in the mediastinum (n=7) or with scintigraphic/US findings discordant for the presence of a cervical EPG (scan positive, US negative or doubtful) (n=14), a tomographic (SPET) acquisition was also obtained. A dual-head gamma camera (Axis, Picker International, Cleveland, Ohio) equipped with a parallel-hole low-energy ultra-high-resolution collimator was used, adopting the following parameters: elliptical orbit, 120 steps, 30 s per step, 64×64 matrix. Tomographic images were reconstructed using a low-pass filter, cut-off 0.2, order 5.0–6.0, and processed using a dedicated computer (Odyssey 830 Digital, Maynard, Mass.). Three-dimensional analysis was also performed.

Two nuclear medicine physicians independently interpreted the scintigraphic images. In the event of discrepancy, the final diagnosis was reached by consensus.

Neck US was performed in the same session as the scintigraphy, using a small-parts, high-resolution 10-MHz transducer (Diasonic, Les-Vlis, France). Longitudinal and transverse neck US scans were obtained from the level of the angle of the mandible to the sternal notch. EPG was identified on grey-scale imaging by the characteristic appearance of a hypoechoic nodule distinct from the thyroid tissue. The US interpretative criteria were as follows: (1) a US examination showing a single hypoechoic nodule distinct from the thyroid gland was considered indicative of a solitary parathyroid adenoma, (2) a US examination showing two or more hypo-

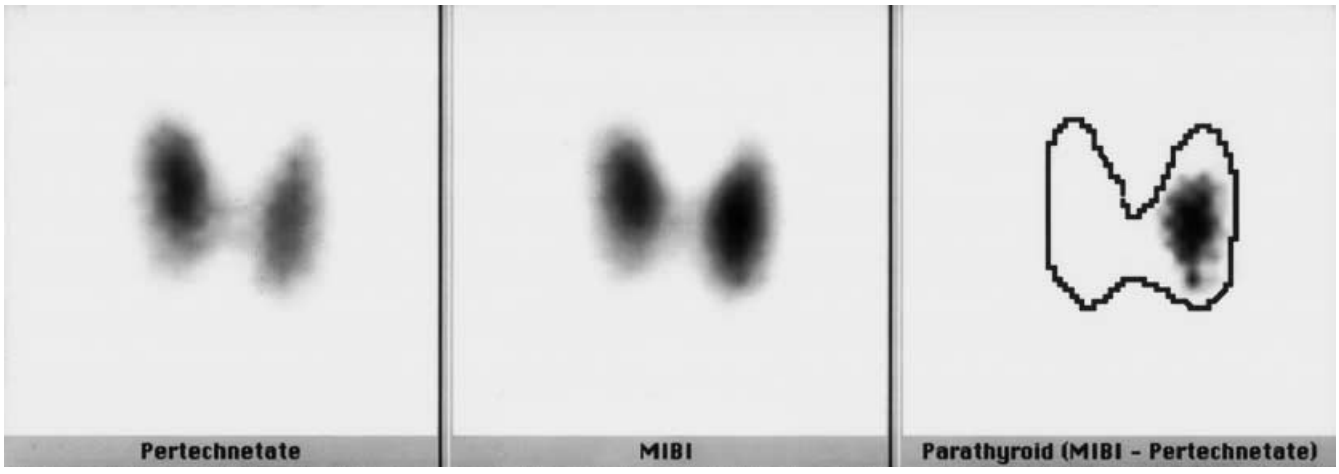

Fig. 1. The $^{99m}TcO_4$ scan shows a normal thyroid gland. The MIBI scan and the MIBI/$^{99m}TcO_4$ subtraction image reveal a single parathyroid adenoma located behind the left thyroid lobe

Fig. 2. The $^{99m}TcO_4$ scan shows a normal thyroid gland. The MIBI scan and the MIBI/$^{99m}TcO_4$ subtraction image reveal a single right inferior parathyroid adenoma located beyond the thyroid contour

echoic nodules distinct from the thyroid gland was considered to be indicative of MGD.

On the basis of preoperative scan/US imaging results, patients were divided into four groups:

Group 1 consisted of 91 patients (63.6%) with scan/US evidence of a single EPG and a normal thyroid gland. An example is shown in Fig. 2. Patients with familial HPT or MEN syndrome were excluded from this group. In group 1 patients, limited neck surgery was planned: unilateral neck exploration in 45 cases and, after the introduction of the IMGP technique at our centre, MIRS in 46.

Group 2 consisted of 24 patients (16.8%) in whom scan/US imaging revealed the presence of a single EPG associated with a nodular goitre. Patients with familial HPT or MEN syndrome were excluded from this group. In 19 of these 24 patients, thyroid nodule(s) were visualised in both lobes or in the lobe contralateral to the EPG; thus, bilateral neck exploration was planned with the aim of performing a partial thyroidectomy together with the parathyroidectomy. An example is shown in Fig. 3. In the other five patients, with thyroid nodule(s) visualised only in the lobe ipsilateral to the EPG, unilateral neck exploration was planned with the aim of performing a thyroid lobectomy together with the parathyroidectomy. An example is shown in Fig. 4.

Group 3 consisted of 21 patients (14.7%) in whom scan/US imaging revealed the presence of two or more EPGs, thus indicating MGD. An example is shown in Fig. 5. In six of these patients there was also a co-existent nodular goitre. Moreover, three patients were affected by a MEN syndrome and two had familial HPT. In all patients of this group, bilateral neck exploration was planned with the aim of performing a subtotal parathyroidectomy and, in some cases, also a partial thyroidectomy.

Group 4 consisted of seven patients (4.9%) in whom neither scintigraphy nor US revealed the presence of EPGs. In one patient a nodular goitre was present; another patient was affected by a MEN syndrome. In these patients a bilateral neck exploration was planned with the aim of intraoperatively detecting and removing the EPG(s).

Intraoperative QPTH was routinely measured by immunofluorimetric assay (Liason, Byk Gulden, Italy, normal values 10–54 pg/ml). QPTH was measured just before the beginning of surgical intervention and 10 min after EPG removal: a fall of at

Fig. 3. The $^{99m}TcO_4$ scan shows a nodular goitre with multiple $^{99m}TcO_4$-hot nodules in both lobes. In addition, the MIBI scan and the MIBI/$^{99m}TcO_4$ subtraction image reveal a concomitant single left superior parathyroid adenoma

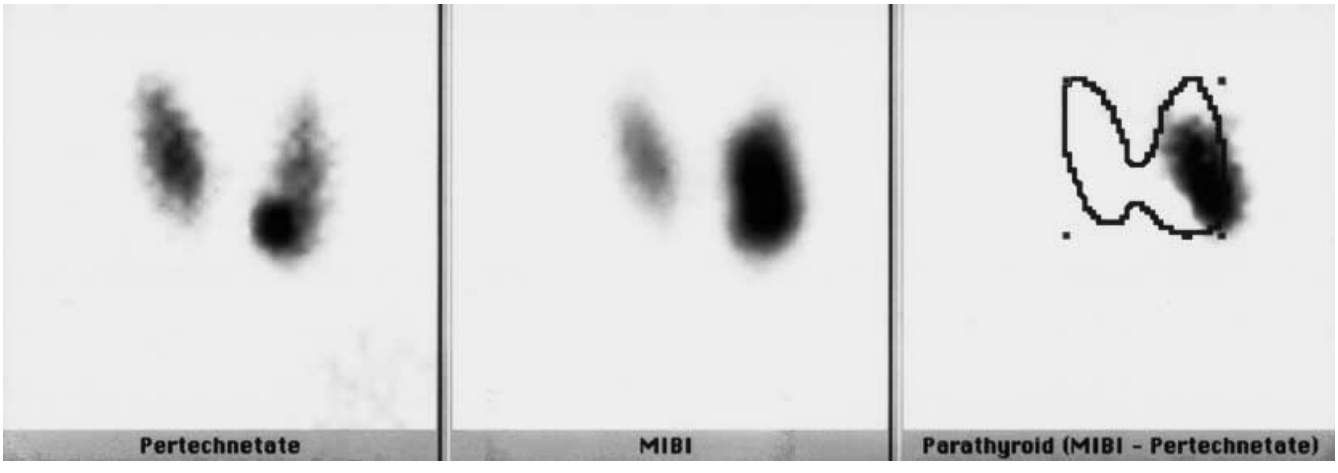

Fig. 4. The $^{99m}TcO_4$ scan shows a single $^{99m}TcO_4$-hot nodule in the lower pole of the left thyroid lobe. In addition, the MIBI scan and the MIBI/$^{99m}TcO_4$ subtraction image reveal a concomitant single parathyroid adenoma located behind the left thyroid lobe

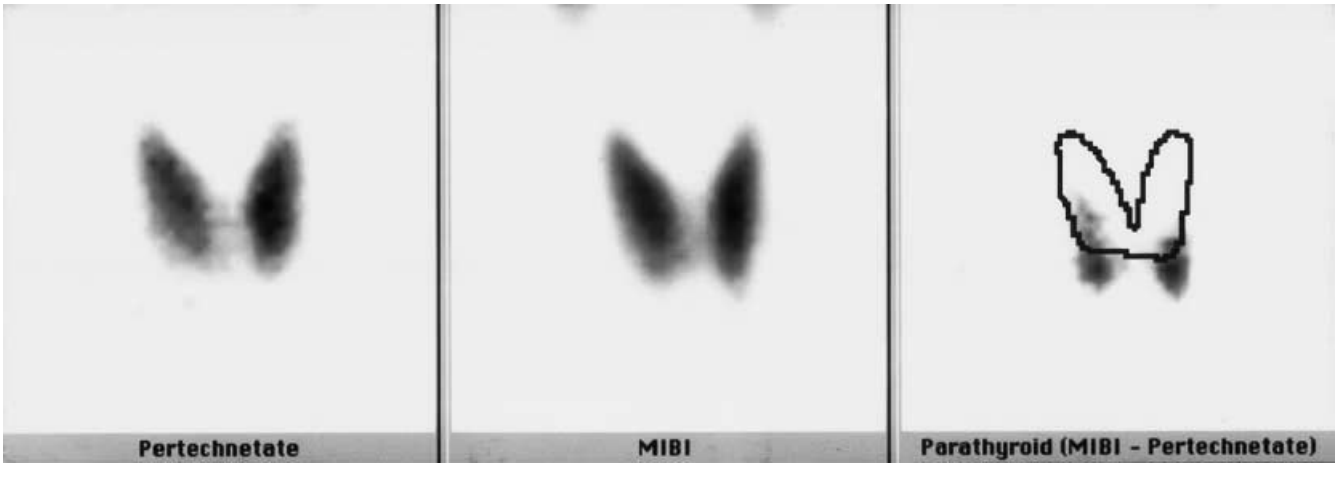

Fig. 5. The $^{99m}TcO_4$ scan shows a normal thyroid gland. The MIBI scan and the MIBI/$^{99m}TcO_4$ subtraction image reveal two inferior enlarged parathyroid glands, one on the right and the other on the left

least 50% in PTH levels compared with the baseline value was considered to confirm successful parathyroidectomy.

Patients received a clinical and laboratory examination 1 month after surgical intervention and this was repeated every 3 months. In cases with suspected disease relapse, neck US and $^{99m}TcO_4$/MIBI scintigraphy were also performed. Post-surgical follow-up ranged from 3 to 46 months (median 20 months).

IMPG technique. The IMGP technique we used has been described in a previous study [13]. The eligibility criteria for MIRS were: (a) evidence of a single EPG at $^{99m}TcO_4$/MIBI scan, and (b) significant MIBI uptake in the EPG. The exclusion criteria were: (a) a negative $^{99m}TcO_4$/MIBI scan, (b) evidence of two or more EPGs on $^{99m}TcO_4$/MIBI scan and/or neck US, (c) the presence of thyroid nodule(s), and (d) a history of MEN or familial HPT. From September 1999 to June 2000, a total of 46 patients (27 females, 19 males, aged 33–72 years, mean 45.3 years) underwent MIRS. The $^{99m}TcO_4$/MIBI scan revealed the EPG to be located beyond the thyroid contour in 31 cases and behind the thyroid gland in 11, to be ectopic in the carotid bifurcation in one, and to be ectopic in the upper mediastinum in four. The IMGP technique consisted of the following steps: (1) in the operative room, during induction of anaesthesia, 37 MBq MIBI was injected, followed by a flush of saline (30 ml) to avoid venous tracer stagnation (initially, 70 MBq of MIBI was injected; subsequently the MIBI dose was progressively reduced to 37 MBq); (2) using the $^{99m}TcO_4$/MIBI scintigraphy images as a guide, the patient's neck was scanned by the surgeon with the probe to determine the cutaneous projection of the EPG; (3) the EPG was detected with the probe and removed through a small, 2- to 2.5-cm, skin incision; (4) radioactivity was measured intraoperatively on the EPG (P), thyroid (T) and background (B) (apex of the lung contralateral to EPG). Radioactivity was also measured in the parathyroid bed (P-bed) after EPG resection to check for residual activity, and in the excised EPG ex vivo to confirm successful parathyroidectomy. P/B, P/T, T/B and P-bed/B ratios were calculated.

A 11-mm hand-held commercially available gamma probe (Scintiprobe 100, Pol.hi.tech., Italy) was used for IMGP.

The labelling efficiency of ^{99m}Tc-MIBI was assessed by thin-layer chromatography and was always greater than 95%.

Data are expressed as mean ± 1 standard deviation (SD). Mean values were compared using Student's *t* test. *P* values less than 0.05 were considered significant. Linear regression analysis was used to evaluate the correlation between the following parameters: parathyroid and thyroid MIBI uptake, parathyroid MIBI uptake and gland size, and MIBI uptake and the time interval from tracer injection to parathyroidectomy.

Results

The preoperative scan/US imaging results and surgical findings are summarised in Table 1. Some aspects for each patient group are worth noting.

Group 1

In 90/91 patients of this group, a single EPG was found at surgery; thus, preoperative imaging was correctly predictive of a single EPG in 98.9% of cases. Moreover, in 87 of these patients (95.6%) a solitary parathyroid adenoma was found at operation, and unilateral neck exploration or MIRS was successfully performed. In all of these cases, QPTH normalised after removal of the parathyroid adenoma. In four patients (4.4%), conversion to bilateral neck exploration was required: in three cases because a parathyroid carcinoma was diagnosed at frozen section histology, and in another patient because the intraoperative QPTH remained elevated after removal of the preoperatively visualised EPG. In this patient a contralateral occult EPG was found at bilateral exploration. In the three patients with parathyroid carcinoma, subtotal thyroidectomy was performed together with the parathyroidectomy: no locoregional metastases were found. In all group 1 patients, serum levels of calcium, phosphorus and PTH remained in the normal range during post-surgical follow-up. Considering the subgroup of 46 patients treated by MIRS, it is worth noting that in 43 of them (93.5%) a solitary parathyroid adenoma was diagnosed at surgery: it was easily detected by the gamma probe and removed through a small, 2- to 2.5-cm, skin incision with a mean operative time of 34 min. The three patients in whom conversion to bilateral neck exploration was required because of intraoperative diagnosis of a parathyroid carcinoma (two cases) or MGD (one case) have been described above.

Group 2

In all 24 patients of this group, a single parathyroid adenoma associated with a nodular goitre was found at surgery, thus confirming the scan/US findings. Concerning the thyroid nodules, frozen section analysis revealed benign nodules in 21 cases, and malignant nodules in three. In these latter three patients, the final histological examination was papillary thyroid carcinoma. Nineteen patients of this group underwent bilateral neck exploration because of the presence of thyroid nodule(s) in both lobes or in the lobe contralateral to the parathyroid adenoma. The other five patients were treated by unilateral neck exploration because the thyroid nodule(s) were present only in the lobe ipsilateral to the parathyroid adenoma. In 23/24 patients, QPTH normalised after parathyroidectomy, and calcium and phosphorus levels remained in the normal range during follow-up. In the remaining patient a mild increase in PTH (ranging from 63 to 74 ng/l), in the presence of normal calcium and phosphorus levels, was observed during follow-up, but repeat neck US and $^{99m}TcO_4$/MIBI scan did not reveal enlarged EPGs.

Group 3

All patients of this group were treated by bilateral neck exploration and in all cases MGD was found at surgery, thus confirming the scan/US findings. Final histological diagnosis was consistent with multiple adenomas in 16 cases and with glandular hyperplasia in five. In six patients, a co-existent nodular goitre was also confirmed

Table 1. Preoperative scintigraphic and US results, and surgical results in our series of 143 patients affected by primary HPT

	Group 1	Group 2	Group 3	Group 4
No. of patients	91 (63.6)	24 (16.8)	21 (14.7)	7 (4.9)
Scan/US findings				
Both scan and US positive	76 (83.5)[a]	19 (79.2)	17 (81.0)	0 (0.0)
Only scan positive	13 (14.3)[b]	3 (12.5)	3 (14.2)	0 (0.0)
Only US positive	2 (2.2)[c]	2 (8.3)[d]	1 (4.8)	0 (0.0)
Surgical findings				
Single parathyroid adenoma	87 (95.6)	24 (100.0)	–	3 (42.9)
Single parathyroid carcinoma	3 (3.3)	–	–	–
Multiple parathyroid adenomas	1 (1.1)	–	16 (76.2)	1 (14.2)
Glandular hyperplasia	–	–	5 (23.8)	3 (42.9)
Concomitant nodular goitre	–	24 (100.0)	6 (28.6)	1 (14.2)
Size of removed parathyroid glands				
Range (mm)	7–50	9–43	8–36	8–21
Mean (SD)	18.9 (7.1)	18.7 (8.6)	16.2 (7.3)	13.1 (4.4)*

Data are reported as mean±1SD. Percentage values are shown in parentheses
Patients were divided into groups 1–4 on the basis of preoperative scintigraphic and US results. Group 1 = patients with scan/US evidence of a single enlarged parathyroid gland and a normal thyroid gland. Group 2 = patients with scan/US evidence of a single enlarged parathyroid gland and a concomitant nodular goitre. Group 3 = patients with scan/US evidence of multiglandular disease (with or without concomitant nodular goitre). Group 4 = patients with both scan and US negative for the presence of enlarged parathyroid glands.
*$P<0.05$
[a] In one patient multiglandular disease was diagnosed at surgery
[b] In 11 patients the parathyroid adenoma was located in an ectopic site (intra- or parathymic in ten, at the carotid bifurcation in one)
[c] Two cases of cystic parathyroid adenoma
[d] Two cases of parathyroid adenoma with concomitant multinodular goitre

at surgery. In 20/21 cases, QPTH normalised after surgery, and calcium and phosphorus levels remained normal during follow-up. Persistent HPT was recorded in one male patient affected by a MEN syndrome. This patient had previously been operated on for a thymic carcinoid in another hospital, and when first seen in our department he presented with hyperthyroidism due to a multinodular goitre associated with HPT; moreover, a 3-cm solid mass in the right adrenal was revealed by CT scan. The patient underwent near-total thyroidectomy and two enlarged EPGs were removed. The right adrenal mass was also removed and diagnosis of paraganglioma was made at histological evaluation. PTH and calcium levels decreased after surgery but did not normalise. A follow-up neck US was negative while scintigraphy revealed an area of MIBI uptake in the right parajugular region suspected to be another EPG. To date, the patient has not undergone further neck surgery.

Group 4

All patients of this group were treated by bilateral neck exploration. At surgery, a solitary parathyroid adenoma (in one case with a concomitant nodular goitre) was found in three cases, multiple adenomas in one and glandular hyperplasia in three. During follow-up no case of persistent or recurrent HPT was observed.

Considering the data altogether, a solitary parathyroid adenoma was diagnosed at surgery in 114 patients (79.7%), MGD in 26 patients (18.2%) and a parathyroid carcinoma in three patients (2.1%). The $^{99m}TcO_4$/MIBI scan correctly depicted a single parathyroid adenoma in 107/114 patients (93.8% sensitivity), MGD in 20/26 patients (76.9% sensitivity) and a parathyroid carcinoma in 3/3 patients (100% sensitivity). The sensitivity of US for the same groups was 83.7% (98/117 cases), 65.4% (17/26 cases) and 100% (3/3 cases), respectively. Among those patients with a single parathyroid adenoma, the $^{99m}TcO_4$/MIBI scan was the only positive examination in 16 patients (11 of whom had an ectopic EPG) while US was the only positive examination in four patients (two with a cystic adenoma and two with a co-existing multinodular goitre). Thus, in patients with a solitary adenoma, the global sensitivity of $^{99m}TcO_4$/MIBI and US imaging was 97.4%. Also in the group of patients with MGD, $^{99m}TcO_4$/MIBI scan and US showed a complementary diagnostic role in four patients, with a global sensitivity of 80.7%.

A nodular goitre co-existed with HPT in 31 patients (21.6% prevalence): 25 of them had a solitary parathy-

Table 2. MIBI tissue ratios, lesion size, operative time and PTH levels in the group of 43 patients treated by MIRS for a solitary parathyroid adenoma

	T/B	P/T	P/B	P-bed/B	Parathyroid adenoma size (mm)[a]	Operative time (min)	PTH pre[b]	PTH post[b]
Range	1.5–1.8	1.1–2.8	1.6–4.0	0.9–1.1	7–50	15–58	76–722	5–46
Mean	1.6	1.5	2.5	1.0	20.1	34.1	189.2	21.3
SD	0.1	0.4	0.5	0.03	8.6	13.5	129.6	11.4

T/B, Thyroid to background ratio; P/T, parathyroid to thyroid ratio; P/B, parathyroid to background ratio; P-bed/B, parathyroid bed (after parathyroid adenoma removal) to background ratio

[a] Maximum diameter

[b] PTH pre, PTH levels measured prior to parathyroidectomy; PTH post, PTH levels measured 10 min after parathyroidectomy; normal PTH values =10–54 pg/ml

roid adenoma, while six had MGD. In all cases, the nodular thyroid disease was correctly diagnosed preoperatively on the basis of the $^{99m}TcO_4$ scan and/or US imaging. Moreover, it must be pointed out that in 30/31 patients (96.7%), the EPGs were correctly depicted despite the presence of nodular goitre.

In contrast to other studies [1, 14], we observed no case of intrathyroid EPG.

SPET results

In five out of seven patients with a mediastinal EGP at planar scintigraphy, SPET located the EPG in anterior slices and surgery confirmed the presence of the EPG within or near the thymus. In the other two patients, SPET located the EPG in posterior slices and, at surgery, the EGP was found in the paratracheal/para-oesophageal space.

In three out of 14 patients with an EGP located in the neck, SPET located the EPG deep in posterior slices and, at surgery, the EPG was found in the paratracheal/para-oesophageal space. In the other 11 patients, SPET located the EPG in anterior slices and surgery confirmed the EGP to lie near the thyroid gland.

IMGP findings

The IMGP results reported here include preliminary data published in a previous report [13]. Table 2 summarises the IMGP results obtained in the group of 43 patients with a solitary parathyroid adenoma evaluated in the present study. Interestingly, the T/B ratio showed a narrow range of variability, suggesting that MIBI uptake is nearly constant in normal thyroid gland. In contrast, a wide range was noted for both P/T and P/B ratios, reflecting wide variability in MIBI uptake by parathyroid adenomas. However, it must be pointed out that the P/B ratio was significantly higher than both the T/B and the P/T ratio ($P<0.01$), and that MIBI uptake was invariably higher in parathyroid adenomas than in normal thyroid tissue. These observations may explain the ease with which parathyroid adenomas were intraoperatively detected by means of the gamma probe. Moreover, in all cases the radioactivity measured in the parathyroid bed after parathyroid adenoma removal fell to values similar to the background activity, suggesting the complete extirpation of hyperfunctioning parathyroid tissue.

Although we did not perform a randomised study, we observed that the operative time was shorter with MIRS than with traditional neck exploration at our centre (average time, 34 min and 75 min, respectively). Furthermore, the length of patient admission was shorter after MIRS than after conventional surgery (1–2 days vs 3–5 days).

No significant correlation was found between the P/B, P/T and T/B ratios, the EPG size, and the time interval from the tracer injection to parathyroidectomy.

Discussion

The classical surgical approach to HPT patients is based on bilateral cervical exploration with the aim of visualising all parathyroid glands and removing those which are enlarged. Furthermore, in some centres, intraoperative biopsy of all parathyroid glands, even if they are of normal size, is performed to investigate for possible MGD. In experienced hands this approach has been demonstrated to be successful in curing primary HPT in 95% of patients, and, due to this high success rate, some authors believe preoperative parathyroid imaging to be unnecessary [2, 3, 4, 5]. However, given that solitary adenoma is the most frequent cause of primary HPT (approximately 85% of cases) [1], extensive bilateral neck exploration may be considered to be an over-treatment for the majority of these patients. In recent years, some authors have reported encouraging results regarding the feasibility of limited, unilateral neck exploration in patients with primary HPT and a high probability of single parathyroid adenoma as judged by preoperative imaging techniques such as scintigraphy and high-resolution US [6, 7, 8, 9]. Furthermore, as already mentioned, the availability of intraoperative QPTH measurements has strongly favoured the unilateral approach, because a rapid and significant decrease in QPTH levels after EGP removal has been proven to be a highly sensitive predictor of successful surgical treatment [10]. At the same time, the introduction into clinical practice of ^{99m}Tc-MIBI has led to a con-

siderable improvement in parathyroid scintigraphic imaging [6, 7, 9, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27]. High sensitivity, around 90%, has been reported with both the single-tracer dual-phase technique and the dual-tracer technique [6, 7, 9, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27]. A major limitation of the single-tracer dual-phase technique is the co-existence of MIBI-avid thyroid nodules that can mimic an EPG and cause false-positive scintigraphic results, thus affecting the specificity of the method [18, 19, 26]. This problem can be overcome, at least in part, by using the dual-tracer scintigraphic technique with either iodine-123 or $^{99m}TcO_4$ as the thyroid agent [7, 9, 12, 13, 15, 16, 17, 21, 22, 23, 24]. Similarly, neck US can be useful in depicting nodular thyroid disease.

In this study, a solitary parathyroid adenoma was found at surgery in 87 of 91 patients (95.6%) with preoperative scan/US visualisation of a single EPG and with a normal thyroid gland. On this basis, limited, unilateral or even minimally invasive neck surgery could be carried out. In three of the91 patients, a single EPG was visualised at preoperative scan/US imaging, but a parathyroid carcinoma was diagnosed at operation and conversion to bilateral neck exploration was consequently required. It is to be noted that neither scintigraphy nor US permitted preoperative diagnosis of a malignant parathyroid lesion and that frozen section analysis was the crucial diagnostic tool in these three patients. In the remaining patient among these 91, MGD was diagnosed at surgery and conversion to bilateral neck exploration was accordingly required. The great importance of intraoperative QPTH assay in this case needs to be underlined: QPTH remained elevated after removal of the preoperatively visualised EPG, thus suggesting the persistence of hyperfunctioning parathyroid tissue, and a contralateral occult EPG was removed.

The most frequent causes of exclusion from limited neck exploration in our series were the co-existence of a nodular goitre and/or evidence of MGD (n=45, 31.5%), while in a minority of cases (n=7, 4.9%) the cause was negative results of both scintigraphy and US. It is interesting that the integrated scan/US imaging protocol which we used proved accurate in distinguishing solitary parathyroid adenoma from MGD, even in the presence of concomitant thyroid nodular disease. It should be noted that although the majority of patients with a solitary parathyroid adenoma and a co-existing nodular goitre underwent bilateral neck exploration, in five cases the preoperative scan/US imaging visualised thyroid nodule(s) only in the lobe ipsilateral to the EPG: this allowed unilateral neck exploration to be undertaken, and the performance of thyroid lobectomy in conjunction with the parathyroidectomy. In light of these considerations, dual-tracer scintigraphy combined with neck US appears to be the imaging protocol of choice for preoperative evaluation of patients with HPT, particularly in geographical areas with a high prevalence of nodular goitre.

A SPET acquisition was obtained only in a selected group of 21 patients with a mediastinal EPG or with incongruent scintigraphic/US findings for the presence of a cervical EPG. Interestingly, in some of these patients, SPET was helpful in locating the EPG deep in the paratracheal or para-oesophageal space. On the basis of our limited data, it is difficult to draw a conclusion as to whether SPET should be recommended as a routine procedure in parathyroid imaging. In this regard, in a recent study performed by Sfakianakis et al. [26] in a group of 62 consecutive patients with primary or secondary HPT, MIBI SPET revealed a 94% sensitivity for the detection of EPG and the three-dimensional analysis helped the surgeon to improve the efficiency of parathyroidectomy.

Regarding MIRS, in contrast to several other protocols reported in the literature [11, 28] in which a relatively high MIBI dose (370–740 MBq) was injected some hours before surgery to obtain both preoperative scintigraphic imaging and intraoperative gamma probe detection, we injected a very low MIBI dose (37 MBq) in the operating room just before the beginning of the exploration. We used this protocol with the aim of avoiding possible false-negative results related to rapid parathyroid MIBI washout, as has recently been described in some parathyroid adenomas [29, 30], and to minimise the radiation exposure to the surgeon and the operative staff. It is worth noting that although we injected a significantly lower MIBI dose, our results are similar to those reported by Bonjer et al. [28], who injected 370 MBq of MIBI: in particular, the P/B ratio ranged from 1.6 to 4.0 (median 2.5) in our study and from 1.2 to 5.1 (median 2.0) in that of Bonjer et al. [28]. Two other aspects of our IMGP protocol have to be considered. First, the mean value of the P/T ratio was relatively high (1.5), and the EPG was easily detected with the gamma probe. However, in several cases the P/T ratio was rather low (1.1 in four patients). This situation might represent a limitation for the detection of small EPGs closely related to the thyroid tissue. Second, the P/B ratio was very high (mean 2.5); thus, it is likely that the IMGP technique can be particularly useful for the detection of the EPGs which appear clearly distinct from the thyroid contour or are located deep in the neck or ectopically in the mediastinum. Furthermore, radioactivity measurement in the resected EPG ex vivo and in the parathyroid bed after EPG removal provided useful information for the surgeon. In particular, in all patients of the present series the radioactivity measured in the parathyroid bed after EPG resection fell to a value similar to that of background activity (Table 2), suggesting successful parathyroidectomy. Conversely, the persistence of significant radioactivity in the parathyroid bed suggests the persistence of hyperfunctioning tissue.

On the basis of the data from this study, we conclude that:

1. A preoperative imaging protocol including $^{99m}TcO_4$/MIBI scintigraphy and high-resolution neck US appears to be highly accurate in selecting patients with primary HPT for limited, unilateral neck exploration.

2. Contemporaneous imaging of the thyroid and parathyroids by means of dual-tracer scintigraphy and US is strongly recommended for the evaluation of thyroid nodule(s) associated with HPT, particularly in geographical areas with a high prevalence of goitre.
3. SPET can provide the surgeon with useful information when an EPG is located in the mediastinum or deep in the neck.
4. In patients with a normal thyroid gland and a high scan/US probability of a solitary parathyroid adenoma, the gamma probe technique with low MIBI doses appears to be a helpful intraoperative approach to aid in minimally invasive surgery.

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