

^{11}C -methionine PET/CT in $^{99\text{m}}\text{Tc}$ -sestamibi-negative hyperparathyroidism in patients with renal failure on chronic haemodialysis

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Abstract. *Purpose:* Scintigraphic localisation of parathyroid glands is often unsuccessful in patients with renal failure on chronic haemodialysis who have secondary hyperparathyroidism (HPT). The purpose of this study was to investigate the use of ^{11}C -methionine PET/CT to detect hyperfunctioning parathyroid glands in patients with renal failure on chronic haemodialysis who had $^{99\text{m}}\text{Tc}$ -sestamibi-negative HPT.

Methods: ^{11}C -methionine PET/CT was performed in 18 patients (11 women and 7 men, aged 42–79 years; mean age 57.8 years) on haemodialysis for renal failure (2–14 years' duration), with normo-, hypo- or hypercalcaemia and HPT not localised by either dual-tracer $^{99\text{m}}\text{Tc}$ -pertechnetate/ $^{99\text{m}}\text{Tc}$ -sestamibi subtraction scans or dual-phase $^{99\text{m}}\text{Tc}$ -sestamibi scans.

Results: In three of ten patients with normo- or hypo-calcaemic HPT there was increased ^{11}C -methionine accumulation in one gland. Seven of eight patients with hypercalcaemic HPT showed increased uptake: in five of these patients increased ^{11}C -methionine accumulation was present in one gland, while in two it was demonstrated in two glands. All patients also had high-resolution ultrasound of the neck and were treated with subtotal parathyroidectomy, leaving a remnant of the smallest of the four glands. Regardless of their size, all glands with abnormal ^{11}C -methionine parathyroid uptake were removed, and all demonstrated parathyroid hyperplasia. All patients developed post-parathyroidectomy hypoparathy-

roidism and one patient with normocalcaemic HPT relapsed 8 months after surgery.

Conclusion: These data suggest that ^{11}C -methionine PET/CT may be used to identify hyperfunctioning parathyroid glands in non-primary HPT, and especially hypercalcaemic HPT, when conventional $^{99\text{m}}\text{Tc}$ -sestamibi imaging is non-localising.

Keywords: ^{11}C -methionine PET/CT – $^{99\text{m}}\text{Tc}$ -sestamibi – Neck ultrasound – Hyperparathyroidism – Renal failure – Haemodialysis

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Introduction

Parathyroid scintigraphy with methionine was first introduced almost 35 years ago using ^{75}Se -selenomethionine [1–5]. The success of parathyroid localisation was variable, and methods were offered to enhance imaging by incorporating thyroid subtraction with $^{99\text{m}}\text{Tc}$ -pertechnetate and pharmacological manipulation of serum calcium levels [6]. ^{75}Se -selenomethionine imaging was subsequently supplanted by more efficacious radiopharmaceuticals like ^{201}Tl , $^{99\text{m}}\text{Tc}$ -sestamibi (MIBI), $^{99\text{m}}\text{Tc}$ -tetrofosmin and variations of MIBI or $^{99\text{m}}\text{Tc}$ -tetrofosmin imaging using thyroid subtraction with ^{123}I or $^{99\text{m}}\text{Tc}$ or, more recently, dual-phase MIBI or $^{99\text{m}}\text{Tc}$ -tetrofosmin scans [7–10]. The availability of the positron-emitting radioisotope ^{11}C has allowed a re-evaluation of methionine as a parathyroid imaging agent, taking advantage of the increased resolution afforded by positron emission tomography (PET), and ^{11}C -methionine has been used to identify hyperfunctioning parathyroid tissues in primary, secondary and recurrent

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Table 1. ¹¹C-methionine PET/CT results in 18 patients with ^{99m}Tc-sestamibi-negative non-primary hyperparathyroidism

Patient no.	Gender	HPT type	Duration of dialysis (yrs)	Serum calcium (mg/dl ^a)	Serum PTH (pg/ml)	MIBI scan results	Ultrasound results	¹¹ C-methionine PET/CT results	SUV (parathyroid cervical soft tissue)	SUV (parathyroid tissue/thyroid tissue)	¹¹ C-methionine-avid gland (mg)	Largest removed gland (mg)	Surgery
1	F	Hypercalcaemic	7	12.1	478	Negative	3 glands	1 gland	4.9	3.6	180	340	Subtotal parathyroidectomy
2	M	Hypercalcaemic	6	11.0	320	Negative	2 glands	1 gland	3.1	2.4	470	470	Subtotal parathyroidectomy
3	M	Hypercalcaemic	3	11.2	229	Negative	2 glands	1 gland	3.0	2.2	250	720	Subtotal parathyroidectomy
4	F	Hypercalcaemic	5	11.7	124	Negative	4 glands	2 glands	4.6, 2.3	3.2, 1.9	640, 310	640	Subtotal parathyroidectomy
5	F	Hypercalcaemic	14	11.2	185	Negative	3 glands	2 glands	4.2, 2.1	2.8, 1.5	530, 370	530	Subtotal parathyroidectomy
6	F	Hypercalcaemic	3	12.6	432	Negative	2 glands	1 gland	2.2	1.7	450	450	Subtotal parathyroidectomy
7	F	Normocalcaemic	8	10.1	1900	Negative	2 glands	1 gland	4.9	3.1	340	810	Subtotal parathyroidectomy
8	M	Hypercalcaemic	4	12.3	340	Negative	2 glands	Negative	-	-	390	390	Subtotal parathyroidectomy
9	F	Hypocalcaemic	3	8.3	435	Negative	2 glands	Negative	-	-	370	370	Subtotal parathyroidectomy
10	M	Hypocalcaemic	6	8.4	396	Negative	3 glands	1 gland	2.8	1.9	270	540	Subtotal parathyroidectomy
11	M	Normocalcaemic	4	9.5	400	Negative	2 glands	Negative	-	-	630	630	Subtotal parathyroidectomy
12	M	Hypocalcaemic	7	7.8	790	Negative	3 glands	1 gland	2.9	2.5	590	590	Subtotal parathyroidectomy
13	F	Normocalcaemic	2	9.1	290	Negative	2 gland	Negative	-	-	560	560	Subtotal parathyroidectomy
14	F	Hypercalcaemic	5	12.2	340	Negative	3 glands	1 gland	4.5	3.4	380	380	Subtotal parathyroidectomy
15	F	Normocalcaemic	4	8.8	540	Negative	2 glands	Negative	-	-	410	410	Subtotal parathyroidectomy
16	M	Normocalcaemic	7	8.6	720	Negative	2 glands	Negative	-	-	320	320	Subtotal parathyroidectomy
17	F	Normocalcaemic	2	9.1	480	Negative	3 glands	Negative	-	-	580	580	Subtotal parathyroidectomy
18	F	Normocalcaemic	4	9.8	1100	Negative	2 glands	Negative	-	-	450	450	Subtotal parathyroidectomy

Columns 12 and 13 show the weight (mg) of resected ¹¹C-methionine-avid parathyroid glands (column 12) and of the largest gland found at surgery (column 13)

F female, M male, HPT hyperparathyroidism, PTH serum parathyroid hormone, SUV standardised uptake value

^aTo convert values to mmol/l, multiply by 0.2495

hyperparathyroidism [11–14]. In this study we investigated the value of ^{11}C -methionine PET/CT in a small group of patients with renal failure on chronic dialysis who had normo-, hypo- or hypercalcaemic hyperparathyroidism and non-localising conventional parathyroid scintigraphy with either MIBI/ $^{99\text{m}}\text{Tc}$ subtraction or dual-phase MIBI imaging studies.

Materials and methods

Eighteen patients [11 women and 7 men, aged 42–79 years (mean 57.8 years)] with non-primary hyperparathyroidism were studied with ^{11}C -methionine PET/CT scans. The study was approved by the Human Experimentation Committee (IRB), and each patient provided written informed consent prior to PET/CT. Ten patients had normo- or hypocalcaemic hyperparathyroidism and eight, hypercalcaemic hyperparathyroidism, the diagnosis being made on the basis of the relationship between serum calcium and parathyroid hormone levels (Table 1). All patients had been treated with haemodialysis for renal failure for 2–14 years.

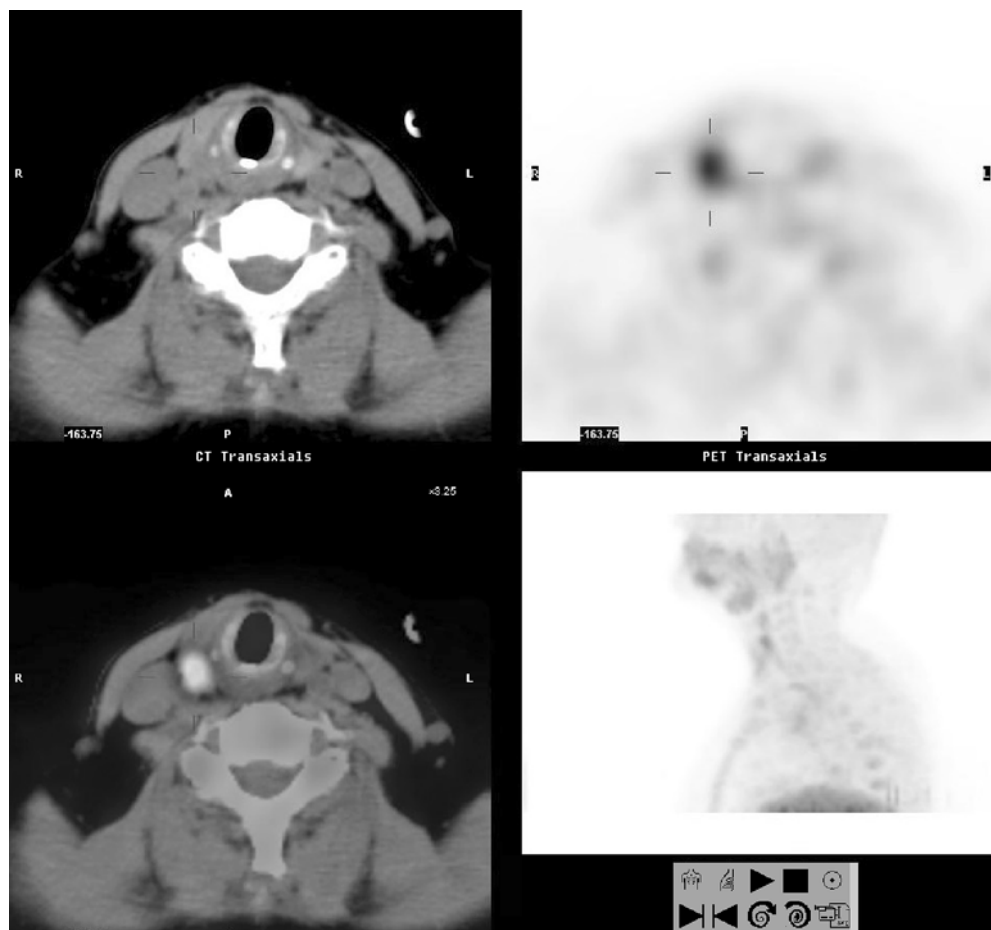
Initial parathyroid imaging was performed in two centres (the S. Orsola-Malpighi Hospital, Bologna, Italy and the S. Maria della Misericordia Hospital, Rovigo, Italy), using dual-tracer $^{99\text{m}}\text{Tc}$ -pertechnetate/ $^{99\text{m}}\text{Tc}$ -sestamibi (MIBI) subtraction scanning in ten patients and dual-phase $^{99\text{m}}\text{Tc}$ -sestamibi imaging in eight cases, employing previously described methods [15]. High-resolution ultrasound of the neck was also performed with 7.5- to 10-MHz transducers, and parathyroid glands were identified as hypochoic

areas located near the thyroid gland that had well-defined margins and were distinct from thyroid tissue. PET was performed with a dedicated PET/CT tomograph (Discovery 4ST, GE Corporation, Milwaukee, WI, USA) 10 min after the intravenous injection of 370–444 MBq (10–12 mCi) of ^{11}C -methionine. Images of the neck and thorax were obtained in three consecutive bed positions, each of 4-min duration, from the base of the skull to the diaphragm. The standardised uptake value (SUV) was calculated using the region of interest (ROI, 3×3 pixels, matrix 128×128) method and was corrected for weight and height.

L-[S-methyl- ^{11}C]-methionine (^{11}C -methionine) was synthesised according to the solid phase method, as described by Pascali et al. [16] Briefly, $^{11}\text{CO}_2$ produced by a PET-trace cyclotron (GE Medical Systems, Milwaukee, WI, USA) was converted into $^{11}\text{CH}_3\text{I}$ by the conventional LiAlH_4 /HI reaction. $^{11}\text{CH}_3\text{I}$ was used for the methylation of L-homocysteine thiolactone (freshly dissolved in 0.5 M NaOH in EtOH/ H_2O 50/50) directly placed on solid phase support (tC18 Plus SepPak, Waters, Milford, MA, USA). L-[S-methyl- ^{11}C]-methionine was eluted with 2.5 ml of 0.05 M NaH_2PO_4 in the collecting vial containing 4.2 ml of saline and 3.3 ml of the same eluting buffer, sterilised by passage through a 0.22- μm filter and collected in a sterilised vial with a final volume of 10 ml. The duration of synthesis was 14 min and the radiochemical yield was 72%. Evaluation of radiochemical purity was done using radio-HPLC equipped with a reversed-phase column, and the concentration of organic solvents was assessed by gas chromatography. Endotoxin content was measured by a conventional limulus amoebocyte lysate (LAL) method (Cambrex Bioscience, East Rutherford, NJ, USA).

PET/CT interpretations were performed by three nuclear medicine physicians (S.F., C.N., D.R.) with extensive experience in both

Fig. 1. Right inferior parathyroid gland depicted by ^{11}C -methionine (patient 6, hypercalcaemic hyperparathyroidism; Table 1). *Upper left*, CT scan; *upper right*, ^{11}C -methionine PET scan [SUV (parathyroid tissue/cervical soft tissue)=2.2]; *lower left*, ^{11}C -methionine PET/CT fusion image; *lower right*, right sagittal ^{11}C -methionine PET scan of the neck



parathyroid and PET imaging; scan interpretations were done independently and there were no discrepancies amongst the readers, i.e. they agreed on all the pathological glands that were seen.

Intact parathyroid hormone was measured by the immunochromiluminescent method (Liason, Byk Gulden, Italy; normal range 10–54 pg/ml). The normal range of serum calcium levels was considered to be 8.4–10.5 mg/dl.

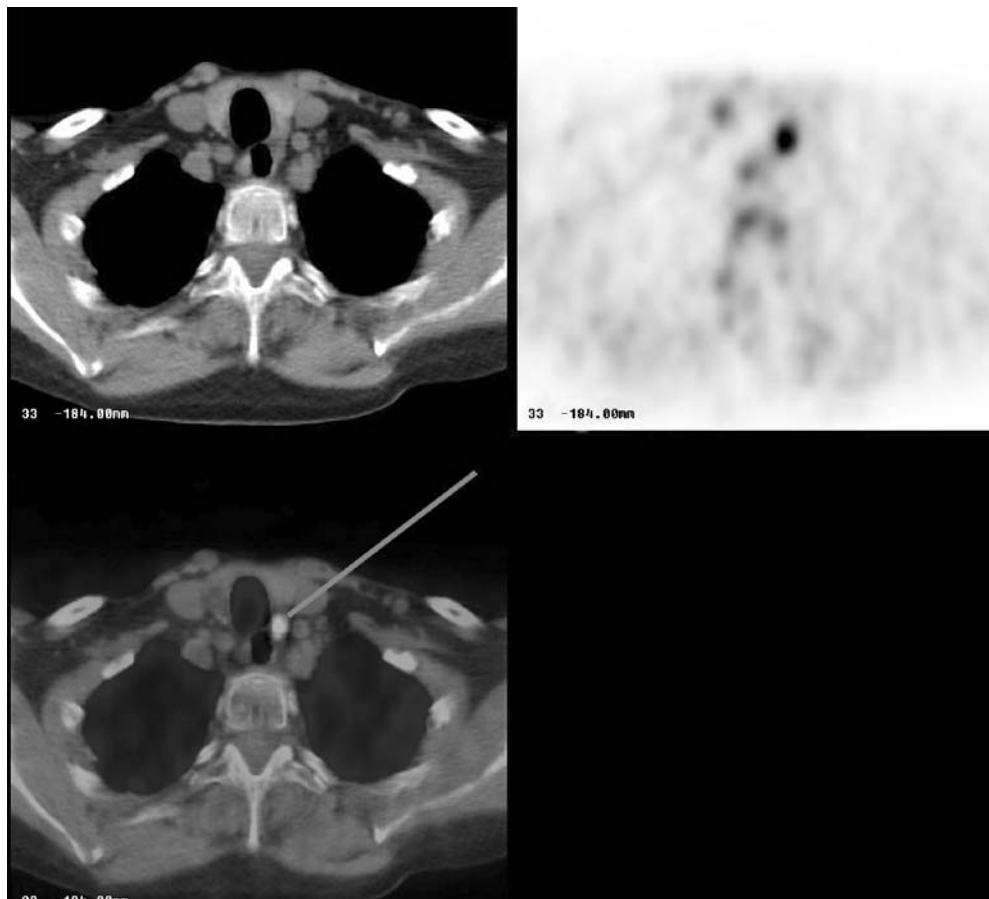
Results

Serum calcium levels were normal or low (mean 8.9 mg/dl, range 7.8–10.1 mg/dl) and parathyroid hormone levels were elevated (mean 705 pg/ml, range 290–1,900 pg/ml) in 10 of 18 patients, while in 8 of 18 patients both calcium and parathyroid hormone levels were elevated (mean 11.8 mg/dl, range 11.0–12.6 mg/dl, and 306 pg/ml, range 124–478 pg/ml, respectively) (Table 1).

Among the 18 patients, high-resolution ultrasound identified two enlarged parathyroid glands in 11, three glands in six and four enlarged glands in one (Table 1). In ten of the 18 patients (55.5%), PET/CT demonstrated abnormal accumulation of ^{11}C -methionine (one parathyroid gland in eight patients and two glands in two patients) (Table 1). Mean SUV(parathyroid tissue/cervical soft tissue) was 3.3 (range 2.1–4.9) and mean SUV(parathyroid tissue/thyroid tissue) was 2.5 (range 1.5–3.6). There was no significant difference in parathyroid gland ^{11}C -methionine

SUVs between the group with normal or low calcium levels and the group with hypercalcaemic hyperparathyroidism. It is of note that in patients with normo- or hypocalcaemic hyperparathyroidism, ^{11}C -methionine PET/CT identified one abnormal gland in only three of ten patients (30%), while in the group with hypercalcaemic hyperparathyroidism, seven of eight patients (87.5%) had abnormal ^{11}C -methionine PET/CT ($p < 0.01$ by χ^2 test). Of the latter seven patients, five had one abnormal gland (Figs. 1, 2) and two, two abnormal glands on PET/CT. The significant difference observed in the rate of detection of abnormal parathyroid glands at ^{11}C -methionine PET/CT in the group of normo- or hypocalcaemic patients versus the group of hypercalcaemic patients might be explained by the fact that in hypercalcaemic patients, that is patients more likely to be affected by tertiary hyperparathyroidism, autonomous parathyroid glands could be biologically more active in trapping ^{11}C -methionine. Further, in four of the ten patients (40%) with abnormal ^{11}C -methionine PET/CT scans (all of whom had hypercalcaemic hyperparathyroidism), the largest parathyroid gland seen on high-resolution ultrasound did not demonstrate the highest ^{11}C -methionine avidity. Comparisons of SUV with serum calcium and parathyroid hormone levels and parathyroid gland weight by regression analysis did not reveal statistically significant differences. No patient had co-existing thyroid nodules in the present series.

Fig. 2. Left superior parathyroid gland depicted by ^{11}C -methionine (patient 1, hypercalcaemic hyperparathyroidism; Table 1). *Upper left*, CT scan; *upper right*, ^{11}C -methionine PET scan [SUV(parathyroid tissue/cervical soft tissue)=4.9]; *lower left*, ^{11}C -methionine PET/CT fusion image



All patients were treated with subtotal parathyroidectomy. In the majority of patients the remnant parathyroid tissue was from the smallest of the parathyroid glands. All ^{11}C -methionine-accumulating glands were resected, regardless of their size. Pathological evaluation of the resected parathyroid glands was consistent with glandular hyperplasia and there were no differences in the pathological findings between ^{11}C -methionine-avid parathyroid glands and non- ^{11}C -methionine-avid glands.

Postoperative hypoparathyroidism was seen in all patients. Serum calcium and parathyroid hormone measurements were obtained at 1 month and then at 3-monthly intervals after surgery. Follow-up ranged from 3 to 13 months, with a median of 6 months. One case of recurrent hyperparathyroidism was seen in a woman with normocalcaemic hyperparathyroidism (patient 18, Table 1) 8 months after subtotal parathyroidectomy.

Discussion

Contemporary modalities for the localisation of parathyroid glands in patients with hyperparathyroidism provide high-resolution anatomical and functional maps of abnormal hormone secretion. When used in tandem, neck ultrasound and MIBI scintigraphy using various imaging techniques (thyroid subtraction or dual-phase imaging) have been shown to offer an efficacious approach for localisation of offending glands, for preoperative planning and for intra-operative decision making [15, 17–20]. Although controversy remains over the use of scintigraphy in the initial evaluation of primary hyperparathyroidism and even more so over its use for localisation of multiglandular hyperplasia in the context of renal failure, radionuclide imaging is recommended for recurrent disease or disease located outside of the neck [19–24].

The retention of MIBI by parathyroid tissue appears to be related to the predominant cell type (chief versus oxyphil), the density of mitochondria, the presence of P-glycoprotein and other multi-drug resistance proteins and, of course, the inherent spatial resolution of gamma cameras, which limits scintigraphic identification to glands that are generally larger than 500 mg in primary hyperparathyroidism [21]. In addition, the cell cycle may play a role in imaging, especially in secondary hyperparathyroidism, where parathyroid cells are more likely to be in a G_0 or non-growth phase while autonomous parathyroid tissues such as adenomas tend to be in a growth phase (G_2+S) [21]. MIBI has been used to depict abnormal parathyroid response to vitamin D therapy in patients with renal failure on chronic haemodialysis as a means to identify glands refractory to therapy with selective parathyroidectomy aimed at preserving parathyroid function [22].

Other tracers have been used with some success for parathyroid localisation, such as ^{18}F -fluorodeoxyglucose (FDG), which depicts the process of glucose accumulation and phosphorylation. However, when using FDG, the specificity is lower owing to the normal accumulation of

the tracer by the thyroid and other benign and malignant processes in the neck [25, 26].

An alternative to conventional single-photon imaging agents like MIBI and FDG is methionine, an agent that had demonstrated some value for parathyroid imaging when labelled with ^{75}Se , and can now be labelled with an alternative, positron-emitting isotope, ^{11}C [11–14]. The mechanisms of accumulation of methionine, a neutral amino acid, by parathyroid tissues are transmembrane amino acid transport, protein synthesis and methionine donor transmethylation [11, 14]. Previous studies in hyperparathyroidism demonstrated that accumulation of ^{11}C -methionine correlated with serum parathyroid hormone and calcium levels and measurements of SUV, and it was estimated that the lower limit of detection of parathyroid adenoma by ^{11}C -methionine PET is ~200 mg [12, 14]. Further, these reports noted that, in comparison with adenomas, parathyroid hyperplasia exhibited a lower SUV and other measurements of methionine transport. Lower accumulation of ^{11}C -methionine in hyperplastic glands and the small number of cases in our series, as compared with other studies, may account for the lack of a statistically significant relationship between SUV and parameters of parathyroid hyperfunction and the weight of the resected glands [13, 14]. Although the number of cases studied with ^{11}C -methionine PET to date is small, its efficacy in localising hyperfunctioning glands in hyperparathyroidism appears superior to that of MIBI [12–14, 23]. Unfortunately, ^{11}C has a short half-life (~20 min), necessitating close proximity to a source of isotope and the synthetic capacity to produce ^{11}C -methionine; this limits its availability to only a few centres.

An interesting aspect of the present study is the use of a hybrid PET/CT tomograph to evaluate the potential role of ^{11}C -methionine in visualising MIBI-negative enlarged parathyroid glands in patients with secondary and tertiary hyperparathyroidism. Very recently, Biggs and Hain [27] reported a similar study, though with a PET scanner, in which the role of ^{11}C -methionine in visualising MIBI-negative or equivocal parathyroid adenomas in patients with primary hyperparathyroidism was assessed. These authors found ^{11}C -methionine PET to have a sensitivity of 83%, a specificity of 100% and an accuracy of 88% in a group of 51 patients evaluated retrospectively. The authors concluded that ^{11}C -methionine PET scanning is valuable in patients with primary hyperparathyroidism in whom conventional imaging techniques have failed to localise the adenoma before proceeding to surgery, or in whom surgery has been performed but has failed to correct the hyperparathyroidism.

In the present, admittedly small series, CT appeared to add little to the functional localisation information derived from the pattern of ^{11}C -methionine uptake on PET imaging alone. CT has also appeared to be of limited supplementary value in studies using combined MIBI SPECT/CT, although SPECT itself has been found to offer some increase in resolution over planar studies in primary and recurrent hyperparathyroidism [28, 29]. The reasons for the lack of

benefit from additional CT information are obscure, since high-resolution ultrasound was successful in identifying multiple glandular abnormalities in these patients. It is possible that no substantial incremental benefit is to be derived from direct anatomical correlation when hyperfunctioning parathyroid glands are small, as in most cases (this is especially true of hyperplastic glands), and when a radiopharmaceutical with high specificity is deployed to evaluate abnormal function in a very small, circumscribed region. However, the presence of thyroid pathology, i.e. multinodular goitre, has an effect upon the efficacy of MIBI imaging in hyperparathyroidism since thyroid adenomas and carcinomas will accumulate MIBI, resulting in a reduction in specificity in the search for parathyroid disease. In this context, high-resolution CT should have some value in distinguishing parathyroid from non-parathyroid MIBI-accumulating lesions. This is less apparent for ^{11}C -methionine PET/CT, but larger studies in patients with underlying thyroid pathology will be needed to answer this question. Our data confirm the results of others that ^{11}C -methionine PET can be used to identify hyperactive parathyroid glands in patients with non-primary hyperparathyroidism not detected by conventional single-photon imaging techniques and that autonomously functioning glands are more readily depicted than functional hyperplasia [13, 14]. Further, we noted discordance between the size of some parathyroid glands seen on high-resolution ultrasound and their functional abnormality depicted by ^{11}C -methionine PET, which was also reflected in the absence of a relationship between the SUV and serum calcium and parathyroid hormone. While the numbers of patients in this series are small, the data offer interesting insights into the possibility of using ^{11}C -methionine accumulation to identify the most functionally abnormal parathyroid glands in patients with non-primary hyperparathyroidism and perhaps those glands that are becoming or are already autonomous. This knowledge would be most useful in predicting the course of development in the natural history of secondary hyperparathyroidism and, more importantly, in choosing the optimal time for selective and limited surgical intervention.

Another limitation of our study is that each patient was scanned only once with ^{11}C -methionine PET, thus providing only a single "snapshot" of parathyroid function in what is obviously a continuum from normal to hyperplasia to autonomy, the time course of which may differ between individual patients and individual parathyroid glands. Despite the shortcomings of the present study, ^{11}C -methionine uptake in a parathyroid gland appears to predict hyperfunction in hypercalcaemic hyperparathyroidism and in some patients with normo- or hypocalcaemic hyperthyroidism, as it does in primary hyperparathyroidism. Our results demonstrate that size may not be the best determinant of dysfunction and perhaps autonomy and suggest that ^{11}C -methionine PET may provide additional information in the evaluation of patients with non- $^{99\text{m}}\text{Tc}$ -MIBI-avid parathyroid disease.

In conclusion, the data of the present study suggest that ^{11}C -methionine PET/CT may be used to identify hyperfunctioning parathyroid glands in non-primary hyperparathyroidism, and especially hypercalcaemic hyperparathyroidism, when conventional $^{99\text{m}}\text{Tc}$ -sestamibi imaging is non-localising.

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