Preoperative parathyroid gland localization with technetium-99m sestamibi in secondary hyperparathyroidism

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Abstract. Technetium-99m sestamibi scintigraphy has become a valuable tool in locating parathyroid glands in patients with primary hyperparathyroidism. The aim of this study was to evaluate its usefulness in secondary hyperparathyroidism. Twenty patients were injected intravenously with 740 MBq of ^{99m}Tc-sestamibi and images were obtained at 15 min and 2 h post injection. All patients underwent parathyroid ultrasonography (US) as well as bilateral surgical neck exploration and 64 parathyroid glands were removed. US revealed at least one enlarged gland in 15/20 patients (75%), while ^{99m}Tc-sestamibi scintigraphy showed focal areas of increased uptake in at least one gland in 17/20 patients (85%). When imaging results for all glands were evaluated according to surgical results, sensitivity was 54% for parathyroid scintigraphy and 41% for US, and specificity was 89% for both imaging techniques. There was a discrepancy between the two imaging modalities in 28 glands (35%). The mean surgical weight of US-positive glands (1492±1436 mg) was significantly higher than that of US-negative glands (775±703 mg) (P<0.05). However, there were no significant differences in weight between sestamibi-positive and sestamibi-negative glands. When only sestamibi-positive glands were considered, a positive correlation between uptake and weight was found (r=0.4, P<0.05). In conclusion, parathyroid US and ^{99m}Tc-sestamibi scintigraphy are complementary imaging techniques in the preoperative localization of abnormal parathyroid glands in patients with secondary hyperparathyroidism. The limited sensitivity of the techniques means that patients will still require bilateral neck exploration; therefore routine preoperative parathyroid scanning in renal patients is not justified.

Key words: Parathyroid scintigraphy – Secondary Hyperparathyroidism – Technetium-99m sestamibi

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Introduction

Secondary hyperparathyroidism is a frequent complication in chronic renal failure patients. Despite the use of active vitamin D metabolites and phosphate binders it is sometimes difficult to control and, unfortunately, with the increasing duration of dialysis, more patients require parathyroidectomy.

The most important factor in achieving a successful surgical outcome is having a surgeon experienced in parathyroid surgery. The second most important factor is the localization of all the parathyroid tissue, but it is frequently difficult to determine where hyperfunctioning tissue is located. Different imaging techniques such as high-resolution ultrasonography, computed tomography (CT), arteriography, magnetic resonance imaging and nuclear medicine procedures have been used for this purpose [1]. Among the different techniques available for parathyroid radionuclide imaging, the most commonly used has been a dual-radioisotope procedure combining thallium-201 with technetium-99m pertechnetate or iodine-123 [2–4]. However, there are some controversies regarding the optimal technical aspects of this procedure, including the order of injection of the radiotracers and the computer subtraction and alignment techniques.

In recent years, ^{99m}Tc-sestamibi scintigraphy has been used for the localization of parathyroid glands as an alternative to ^{201}Tl/^{99m}Tc subtraction scintigraphy [5], and an approach which relies on the administration of a single dose with a double-phase imaging procedure has been proposed [6]. Recently it has been reported that this technique is a valuable tool in patients with primary hyperparathyroidism for the preoperative evaluation of a first exploration [7] as well as before reoperation [8]. However, the data so far from patients with secondary hyperparathyroidism are very limited.

The aim of this study was to evaluate the usefulness of double-phase ^{99m}Tc-sestamibi scintigraphy in the preoperative assessment of patients with secondary hyperparathyroidism.

Materials and methods

Patients. The study group included 20 patients (9 males, 11 females; mean age 48 years, range 28–78), all of whom had clinical, biochemical and radiological evidence of secondary hyperparathyroidism. Twelve patients presented chronic renal failure and were on haemodialysis while the remaining eight were renal transplant patients. Parathyroid ultrasonography (US) was performed on all patients and parathyroid size was estimated by measuring the maximum diameter of the gland. All patients underwent bilateral surgical neck exploration and 64 parathyroid glands were removed, weighed and examined histologically.

Parathyroid scintigraphy. The patients were injected intravenously with 740 MBq (20 mCi) of ^{99m}Tc-sestamibi. The labelling efficiency was previously assessed by thin layer chromatography. Radiochemical purity was higher than 95% in all labellings. Anterior views of the neck and the upper thorax were performed with the patient supine. Images were obtained at 15 min (initial or thyroid phase) and 2 h (delayed or parathyroid phase) after the administration of the radiopharmaceutical. A digital gamma camera (Elscint SP4-HR) with a low-energy, high-resolution, parallel-hole collimator was used.

The scans were interpreted visually by two blinded nuclear medicine physicians without previous knowledge of the patients'

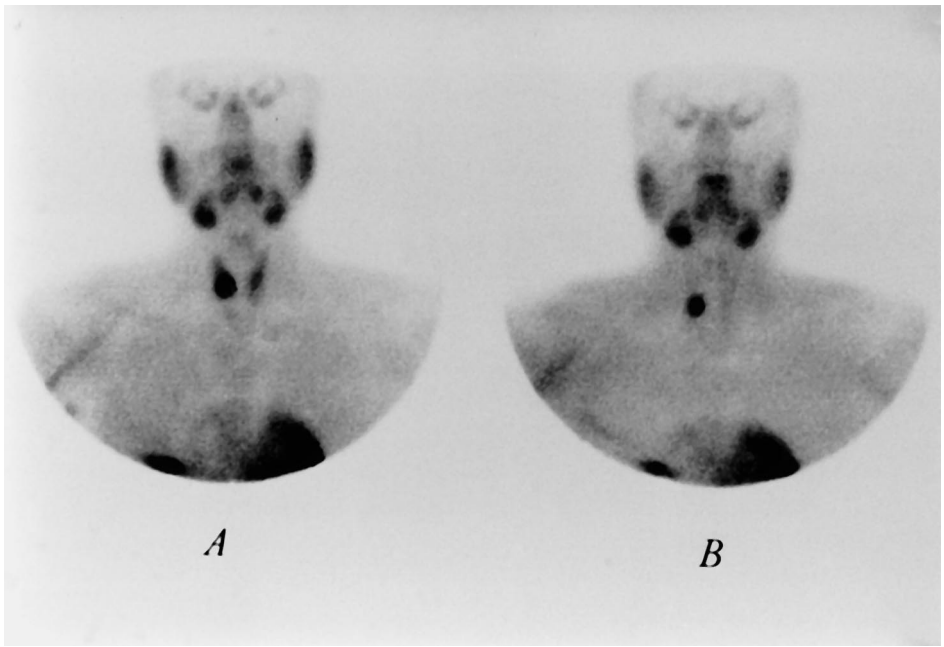

Fig. 1A, B. Double-phase ^{99m}Tc-sestamibi parathyroid scintigraphy. Images at 15 min (**A**) and 2 h (**B**) post injection. A focal uptake which remains after thyroid clearance (scored as marked uptake) is clearly seen in the inferior right lobe. A pathological gland weighing 1950 mg was removed

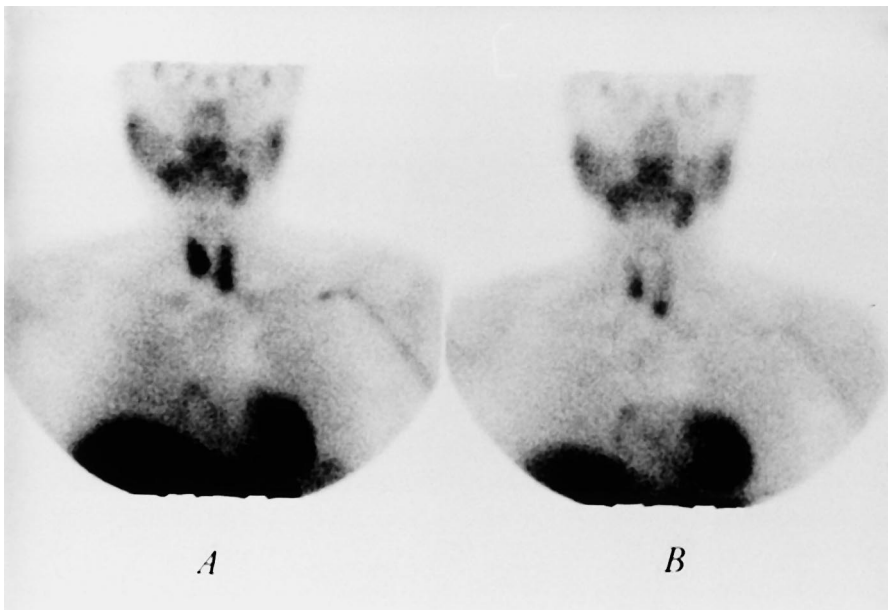

Fig. 2. ^{99m}Tc-sestamibi parathyroid imaging obtained at 15 min (**A**) and 2 h (**B**) post injection. On delayed imaging there are two focal areas of increased activity in both lower poles of the thyroid (which were scored as moderate uptake). During surgery, three hyperplastic glands (weighing 1500, 950 and 240 mg) were found. The gland weighing 240 mg was not seen on scintigraphy and was situated in the upper left pole of the thyroid

Table 1. Diagnostic accuracy of ultrasonography and ^{99m}Tc-sestamibi parathyroid scintigraphy

	TP	TN	FP	FN	Se	Sp	A	PPV	NPV
Ultrasonography	25	17	2	36	41	89	53	93	32
^{99m}Tc-sestamibi	33	17	2	28	54	89	63	94	38

TP, True-positive; TN, true-negative; FP, false-positive; FN, false negative; Se, sensitivity; Sp, specificity; A, accuracy; PPV, positive predictive value; NPV, negative predictive value

data. Focal areas of increased uptake which showed either a relative progressive increase over time or a fixed uptake which persisted on delayed imaging were considered pathological. These areas were scored for activity on a three-point scale: 1=faint uptake, 2=moderate uptake, 3=marked uptake.

Statistical analysis. The Mann-Whitney *U* test was used to compare distributions between two groups. Correlation between parameters was calculated by Spearman's correlation coefficient. Sensitivity and specificity were evaluated by standard methods. A *P* value <0.05 was considered statistically significant.

Results

All patients had increased intact parathyroid hormone (iPTH) serum levels which decreased in all cases after parathyroidectomy.

Table 2. Concordance between ultrasonography and ^{99m}Tc-sestamibi parathyroid scintigraphy imaging results

	Ultrasonography	
	Positive	Negative
Sestamibi		
Positive	17	18
Negative	10	35

Parathyroid US revealed at least one enlarged gland in 15/20 patients (75%), the maximum gland diameter being 2.6 cm. ^{99m}Tc-sestamibi scintigraphy showed focal areas of increased uptake in at least one gland in 17/20 patients (85%) (Figs. 1, 2). Patients with negative scintigraphy had lower iPTH serum levels than patients with positive scintigraphy, although the difference was not statistically significant, probably due to the small number (n=3) of ^{99m}Tc-sestamibi-negative scans.

During surgery, a total of 64 pathological glands were found and all of them were removed. Their weight ranged from 85 to 5300 mg (mean 1050±1092 mg). When imaging results for all glands were evaluated according to surgical results, sensitivity was higher for parathyroid scintigraphy (54%) than for US (41%) and specificity was 89% for both imaging techniques. There were more difficulties in detecting the upper than the lower pathological glands, the number of false-negatives being 20 and 23 in the upper localization and 8 and 13 in the lower localization for US and scintigraphy, respectively. There was a discrepancy between the two imaging modalities in 28 glands (35%). The comparative imaging results are shown in Tables 1 and 2.

The mean surgical weight of US-positive glands (1492±1436 mg) was significantly higher than that of US-negative glands (775±703 mg) (P<0.05). However, there were no significant differences in weight between

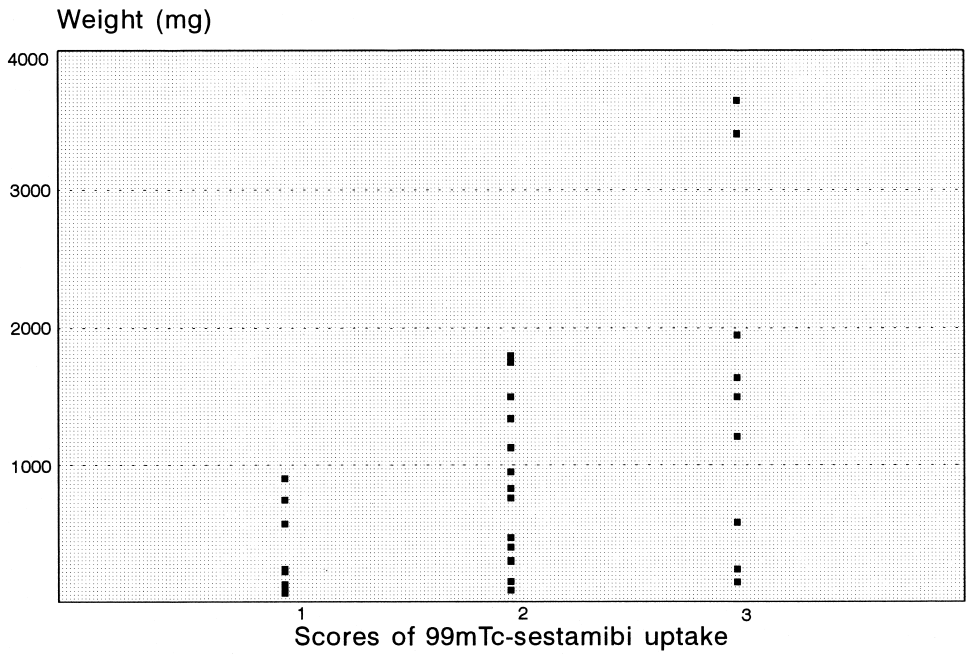

Fig. 3. Scores of ^{99m}Tc-sestamibi uptake and the weight of glands. *1*, faint uptake, *2*, moderate uptake, *3*, marked uptake

sestamibi-positive and sestamibi-negative glands. When only sestamibi-positive glands were considered, a significant positive correlation between the score of uptake and weight was found (r=0.4, P<0.05) (Fig. 3).

Discussion

Although many parathyroid surgeons question the necessity for imaging before a first operation [9, 10], parathyroid surgery is itself changing, with a trend towards more limited neck exploration which requires localization of the glands preoperatively [11].

Several imaging techniques can be performed to locate abnormal parathyroid glands. CT and magnetic resonance imaging are not commonly used. US has been extensively used but with a wide variation in the reported sensitivity. Radionuclide parathyroid imaging has also shown a wide range of results, ^{201}Tl/^{99m}Tc pertechnetate subtraction scintigraphy being the most commonly used technique until ^{99m}Tc-sestamibi was introduced [5]. This radiopharmaceutical has been recommended for subtraction scintigraphy using either ^{123}I or ^{99m}Tc-pertechnetate as thyroid tracers [12–14] as well as for the double-phase approach using a single dose [6]. Several studies have demonstrated better results for ^{99m}Tc-sestamibi than for ^{201}Tl and other imaging techniques [7, 14–16], especially in those cases with ectopic glands [17].

Double-phase parathyroid scintigraphy with ^{99m}Tc-sestamibi has been reported to be a valuable tool in exploring patients with primary hyperparathyroidism, showing a high sensitivity of detection for adenomas (83%–95%) but lower detection rates for hyperplastic glands [7, 18, 19]. Extensive studies using double-phase scintigraphy with ^{99m}Tc-sestamibi have not yet been published in the preoperative assessment of uraemic patients with secondary hyperparathyroidism, which was the aim of this study. In a previous study 38 patients with chronic renal failure were studied but only nine underwent surgical neck exploration [20]. All our patients underwent surgery and a total of 64 parathyroid glands were removed. Sensitivity was higher for parathyroid scintigraphy (54%) than for US (41%) but appeared to be unsatisfactory for both techniques in the complete localization of pathological glands in these patients. Although ^{99m}Tc-sestamibi scintigraphy showed focal areas of increased uptake in at least one gland in 85% of the patients, the sensitivity was only 54% when all pathological glands were taken into account. Therefore, we agree with previous reports [18, 21] that neither parathyroid scintigraphy nor US is effective enough in the detection of multiglandular disease to allow avoidance of routine bilateral neck exploration.

The high discordance found between scintigraphy and US (35% of the glands) is not surprising. US detection of the glands depends on their size, and we found that the mean surgical weight of US-positive glands was twice that of US-negative glands. The ability of ^{99m}Tc-sestamibi to concentrate within parathyroid glands is probably more directly related to blood flow, but blood flow and metabolic activity may well be related, which explains the absence of differences in weight between sestamibi-positive and sestamibi-negative glands. A recent study has shown a relationship between the gland weight and scintigraphic positivity in the detection of adenomas, but this dependence on gland weight was not found in hyperplasia [22]. In our study group, scintigraphy was not able to detect the largest gland (with a weight of 5300 mg), which could have been due to calcification of the gland with a decrease in its functional activity. Therefore, we agree with Piga et al. [20] that function and size are not necessarily related in secondary hyperparathyroidism and that sestamibi-negative and sestamibi-positive glands of a different size can coexist in most patients. These authors found a significant correlation between parathyroid size and serum iPTH concentrations in sestamibi-positive glands but not in sestamibi-negative glands. In accordance with this finding we found a significant positive correlation between parathyroid weight and the scintigraphic score of uptake in sestamibi-positive glands but not in sestamibi-negative glands.

In conclusion, parathyroid US and ^{99m}Tc-sestamibi scintigraphy are complementary imaging techniques in the preoperative localization of abnormal parathyroid glands in patients with secondary hyperparathyroidism. The limited sensitivity of the techniques means that patients will still require bilateral neck exploration; therefore routine preoperative parathyroid scanning in renal patients is not justified.

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References

1. Coakley AJ. Parathyroid imaging. *Nucl Med Commun* 1995; 16: 522–533.
2. Ferlin G, Borsato N, Camerani M, Conte N, Zotti D. New perspectives in localising enlarged parathyroids by technetium-thallium subtraction scan. *J Nucl Med* 1983; 24: 438–441.
3. Percival RC, Blake GM, Urwin GH, et al. Assessment of thallium-pertechnetate subtraction scintigraphy in hyperparathyroidism. *Br J Radiol* 1985: 58: 131–135.
4. Sandrock D, Dunham RG, Neumann RD. Simultaneous dual energy acquisition for ^{201}Tl/^{99}Tc^{m} parathyroid subtraction scintigraphy: physical and physiological considerations. *Nucl Med Commun* 1990; 11: 503–510.
5. Coakley AJ, Kettle AG, Wells CP, O'Doherty MJ, Collins REC. 99mTc-sestamibi: a new agent for parathyroid imaging. *Nucl Med Commun* 1989; 10: 791–794.
6. Taillefer R, Boucher Y, Potvin C, Lambert R. Detection and localization of parathyroid adenomas in patients with hyperparathyroidim using a single radionuclide imaging procedure with technetium-99m-sestamibi (double-phase study). *J Nucl Med* 1992; 33: 1801–1807.

7. Caixas A, Berna L, Piera J, et al. Utility of ^{99m}Tc-sestamibi scintigraphy as a first-line imaging procedure in the preoperative evaluation of hyperparathyroidism. *Clin Endocrinol* 1995; 43: 525–530.
8. Chen C, Skarulis MC, Fraker DL, Alexander HR, Marx SJ, Spiegel AM. Technetium-99m-sestamibi imaging before reoperation for primary hyperparathyroidism. *J Nucl Med* 1995; 36: 2186–2191.
9. Miller DL. Pre-operative localization and interventional treatment of parathyroid tumors: when and how? *World J Surg* 1991; 15: 706–715.
10. Krubsack AJ, Wilson SD, Lawson TL, et al. Prospective comparison of radionuclide, computed tomographic, sonographic, and magnetic resonance localization of parathyroid tumors. *Surgery* 1989; 106: 639–646.
11. Arkles LB, Jones T, Hicks RJ, De Luise MA, Chou ST. Impact of complementary parathyroid scintigraphy and ultrasonography on the surgical management of hyperparathyroidism. *Surgery* 1996; 120: 845–851.
12. O'Doherty MJ, Kettle AG, Wells P, Collins REC, Coakley AJ. Parathyroid imaging with technetium-99m-sestamibi: preoperative localization and tissue uptake studies. *J Nucl Med* 1992; 33: 313–318.
13. Wei JP, Burke GJ, Mansberger AR. Prospective evaluation of the efficacy of technetium 99m sestamibi and iodine 123 radionuclide imaging of abnormal parathyroid glands. *Surgery* 1992; 112: 1111–1117.
14. Geatti O, Shapiro B, Orsolon PG, et al. Localization of parathyroid enlargement: experience with technetium-99m methoxyisobutylisonitrile and thallium-201 scintigraphy, ultrasonography and computed tomography. *Eur J Nucl Med* 1994; 21: 17–22.
15. Casas AT, Burke GJ, Sathyanarayana AJ, Manberger AR, Wei JP. Prospective comparison of technetium-99m-sestamibi/iodine-123 radionuclide scans versus high-resolution ultrasonography for the preoperative localization of abnormal parathyroid glands in patients with previously unoperated primary hyperparathyroidism. *Am J Surg* 1993; 166: 369–373.
16. Weber CJ, Vansant J, Alazraki N, et al. Value of technetium 99m sestamibi iodine 123 imaging in reoperative parathyroid surgery. *Surgery* 1993; 114: 1011–1018.
17. Berna L, Caixas A, Piera J, et al. Technetium-99m-methoxyisobutylisonitrile in localization of ectopic parathyroid adenoma. *J Nucl Med* 1996; 37: 631–633.
18. Light VL, McHenry CR, Jarjoura D, Sodee DB, Miron SD. Prospective comparison of dual-phase technetium-99m-sestamibi scintigraphy and high resolution ultrasonography in the evaluation of abnormal parathyroid glands. *Am Surg* 1996; 62: 562–567.
19. Billy HT, Rimkus DR, Hartzman S, Latimer RG. Technetium-99m-sestamibi single agent localization versus high resolution ultrasonogrphy for the preoperative localization of parathyroid glands in patients with primary hyperparathyroidism. *Am Surg* 1995; 882–888.
20. Piga M, Bolasco P, Satta L, et al. Double-phase parathyroid technetium-99m-MIBI scintigraphy to identify functional autonomy in secondary hyperparathyroidism. *J Nucl Med* 1996; 37: 565–569.
21. McHenry CR, Lee K, Saadey J, Neumann DR, Esselstyn CB. Parathyroid localization with technetium-99m-sestamibi: a prospective evaluation. *J Am Coll Surg* 1996; 183: 25–30.
22. Blocklet D, Martin Philippe, Schoutens A, Verhas M, Hooghe L, Kinnaert P. Presurgical localization of abnormal parathyroid glands using a single injection of technetium-99m methoxyisobutylisonitrile: comparison of different techniques including factor analysis of dynamic structures. *Eur J Nucl Med* 1997; 24: 46–51.